IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC., Plaintiff, v. APOTEX, INC. Defendant.	)	C.A. No._____

COMPLAINT FOR PATENT INFRINGEMENT AGAINST APOTEX, INC.

For its Complaint, Plaintiff Merck & Co., Inc. ("Merck") alleges as follows:

THE PARTIES

1. Plaintiff Merck is a corporation incorporated under the laws of New Jersey with its principal place of business at One Merck Drive, Whitehouse Station, New Jersey 08889.

2. On information and belief, Defendant Apotex, Inc. ("Apotex") is a Canadian company with offices at 150 Signet Drive, Toronto, Canada M9L 1T9. It has authorized Apotex Corp., incorporated under the laws of Delaware and with principal place of business at 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326, to act as agent for service of process with respect to commencement of this patent infringement action.

JURISDICTION AND VENUE

3. This action arises under the patent laws of the United States of America and jurisdiction is founded on Title 28, United States Code §§ 1331 and 1338(a).

4. Venue is proper in this Court under Title 28, United States Code §§ 1391(c) and 1400(b), because the defendant has submitted to personal jurisdiction in this judicial district for this action.

BACKGROUND

5. On October 25, 1994, United States Letters Patent No. 5,358,941 (the "'941 patent"), entitled DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS WITH LACTOSE, duly and legally issued to Simon R. Bechard, Kenneth A. Kramer, and Ashok V. Katdare. The '941 patent is currently set to expire on December 2, 2012. The '941 patent discloses and claims novel pharmaceutical compositions of bisphosphonic acids and salts thereof, which are useful in the treatment and prevention of diseases including osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease. A copy of the '941 patent is attached to this Complaint as Exhibit 1.

6. On October 28, 1997, United States Letters Patent No. 5,681,590 (the "'590 patent"), entitled DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS, duly and legally issued to Simon R. Bechard, Kenneth A. Kramer, and Ashok V. Katdare. The '590 patent is currently set to expire on December 2, 2012. The '590 patent discloses and claims novel pharmaceutical compositions and novel processes for manufacturing compositions of bisphosphonic acids and salts thereof, which are useful in

the treatment and prevention of diseases including osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease. A copy of the '590 patent is attached to this Complaint as Exhibit 2.

7. On December 15, 1998, United States Letters Patent No. 5,849,726 (the "'726 patent"), entitled ANHYDROUS ALENDRONATE MONOSIDUM SALT FORMULATIONS, duly and legally issued to Gerald S. Brenner, Drazen Ostovic, Earl R. Oberholtzer, Jr., and J. Eric Thies. The '726 patent is currently set to expire on June 6, 2015. The '726 patent discloses and claims novel pharmaceutical compositions of anhydrous 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt, as well as novel methods for treating and preventing bone loss with these compositions. A copy of the '726 patent is attached to this Complaint as Exhibit 3.

8. On December 28, 1999, United States Letters Patent No. 6,008,207 (the "'207 patent"), entitled ANHYDROUS ALENDRONATE MONOSIDUM SALT FORMULATIONS, duly and legally issued to Gerald S. Brenner, Drazen Ostovic, Earl R. Oberholtzer, Jr., and J. Eric Thies. The '207 patent is currently set to expire on June 6, 2015. The '207 patent discloses and claims novel methods for administering anhydrous alendronate monosodium salt formulations. A copy of the '207 patent is attached to this Complaint as Exhibit 4.

9. On July 18, 2000, United States Letters Patent No. 6,090,410 (the "'410 patent"), entitled ANHYDROUS ALENDRONATE MONOSIDUM SALT FORMULATIONS, duly and legally issued to Simon R. Bechard, Kenneth A. Kramer, and Ashok V. Katdare. The '410 patent is currently set to expire on December 2, 2012. The '410 patent discloses and claims novel pharmaceutical compositions of

bisphosphonic acids and salts thereof, which are useful in the treatment and prevention of diseases including osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease. A copy of the '410 patent is attached to this Complaint as Exhibit 5.

10. On February 27, 2001, United States Letters Patent No. 6,194,004 (the "'004 patent"), entitled DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS, duly and legally issued to Simon R. Bechard, Kenneth A. Kramer, and Ashok V. Katdare. The '004 patent is currently set to expire on December 2, 2012. The '004 patent discloses and claims novel pharmaceutical compositions of bisphosphonic acids and salts thereof, which are useful in the treatment and prevention of diseases including osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease. A copy of the '004 patent is attached to this Complaint as Exhibit 6.

11. On November 30, 1999, United States Letters Patent No. 5,994,329 (the "'329 patent") duly and legally issued to Anastasia G. Daifotis, Arthur C. Santora, II, and John Yates entitled METHOD FOR INHIBITING BONE RESORPTION. The '329 patent is currently set to expire on July 17, 2018. The '329 patent discloses and claims methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects, and pharmaceutical compositions and kits for carrying out these therapeutic methods. A copy of the '329 patent is attached to this Complaint as Exhibit 7.

12. On January 18, 2000, United States Letters Patent No. 6,015,801 (the "'801 patent") duly and legally issued to Anastasia G. Daifotis, A. John Yates, and Arthur C. Santora, II entitled METHOD OF INHIBITING BONE RESORPTION. The '801 patent is currently set to expire on July 17, 2018. The '801 patent discloses and

claims methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects, and pharmaceutical compositions and kits for carrying out these therapeutic methods. A copy of the '801 patent is attached to this Complaint as Exhibit 8.

13. On May 1, 2001, United States Letters Patent No. 6,225,294 (the "'294 patent") duly and legally issued to Anastasia G. Daifotis, Arthur C. Santora, II and John Yates entitled METHOD OF INHIBITING BONE RESORPTION. The '294 patent is currently set to expire July 17, 2018. The '294 patent discloses and claims methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects, and pharmaceutical compositions and kits for carrying out these therapeutic methods. A copy of the '294 patent is attached to this Complaint as Exhibit 9.

14. Merck is the owner through assignment of the '941, '590, '726, '207, '410, '004, '329, '801, and '294 patents. Merck also owns an approved New Drug Application (NDA No. 20-560) for alendronate sodium tablets that are sold under its trademark FOSAMAX®.

15. The publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration ("FDA") under the Federal Food, Drug, and Cosmetic Act. Merck listed the '941, '590, '726, '207, '410, '004, '329, '801, and '294 patents in the Orange Book for its FOSAMAX® tablets.

16. The FDA granted a six-month period of market exclusivity beyond the patent terms for Merck's FOSAMAX® drug product due to the timely submission

and acceptance of pediatric studies pursuant to 21 U.S.C. § 355a(c). This six-month period is also listed in the Orange Book. The FDA may therefore not approve to market generic versions of Merck's FOSAMAX® tablets until six months after the expiration dates of the '941, '590, '726, '207, '410, '004, '329, '801, and '294 patents. The six-month "pediatric exclusivity period" expires on June 2, 2013, for the '941 patent; June 2, 2013, for the '590 patent; December 6, 2015, for the '726 patent; December 6, 2015, for the '207 patent; June 2, 2013, for the '410 patent; June 2, 2013, for the '004 patent; January 17, 2019, for the '329 patent; January 17, 2019, for the '801 patent; and January 17, 2019, for the '294 patent. The FDA also may not approve to market generic versions of Merck's FOSAMAX® tablets until the expiration of all other patents and the subsequent pediatric exclusivity period listed in the Orange Book.

17. On information and belief, an Abbreviated New Drug Application (ANDA No. 077-982) has been filed on behalf of Apotex, including a certification under Title 21, United States Code § 355(j)(2) with the FDA for 5 mg, 10 mg, 35 mg, and 70 mg alendronate sodium tablets. Apotex's ANDA No. 077-982 allegedly contains a certification of invalidity, unenforceability, and/or noninfringement of the '941, '590, '726, '207, '410, '004, '329, '801, and '294 patents. Notice of that certification, but not the certification, was transmitted to Merck on or after February 24, 2006.

18. On information and belief, Apotex filed ANDA No. 077-982 because it seeks to enter the market that FOSAMAX® pharmaceutical products have created due to their benefits and advantages.

COUNT I

19. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

20. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '941 patent, before the expiration of the '941 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

21. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '941 patent, it was aware of the existence of the '941 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

22. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '941 patent.

23. On information and belief, the infringement by Apotex of the '941 patent was and is willful.

24. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

COUNT II

25. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

26. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '590 patent, before the expiration of the '590 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

27. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '590 patent, it was aware of the existence of the '590 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

28. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '590 patent.

29. On information and belief, the infringement by Apotex of the '590 patent was and is willful.

30. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

COUNT III

31. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

32. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '726 patent,

before the expiration of the '726 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

33. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '726 patent, it was aware of the existence of the '726 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

34. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '726 patent.

35. On information and belief, the infringement by Apotex of the '726 patent was and is willful.

36. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

COUNT IV

37. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

38. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '207 patent, before the expiration of the '207 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

39. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '207

patent, it was aware of the existence of the '207 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

40. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '207 patent.

41. On information and belief, the infringement by Apotex of the '207 patent was and is willful.

42. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

COUNT V

43. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

44. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '410 patent, before the expiration of the '410 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

45. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '410 patent, it was aware of the existence of the '410 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

46. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '410 patent.

47. On information and belief, the infringement by Apotex of the '410 patent was and is willful.

48. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

COUNT VI

49. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

50. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '004 patent, before the expiration of the '004 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

51. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '004 patent, it was aware of the existence of the '004 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

52. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '004 patent.

53. On information and belief, the infringement by Apotex of the '004 patent was and is willful.

54. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

COUNT VII

55. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

56. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '329 patent, before the expiration of the '329 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

57. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '329 patent, it was aware of the existence of the '329 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

58. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '329 patent.

59. On information and belief, the infringement by Apotex of the '329 patent was and is willful.

60. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

COUNT VIII

61. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

62. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '801 patent, before the expiration of the '801 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

63. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '801 patent, it was aware of the existence of the '801 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

64. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '801 patent.

65. On information and belief, the infringement by Apotex of the '801 patent was and is willful.

66. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

COUNT IX

67. Each of the preceding paragraphs 1 to 18 is incorporated as if fully set forth.

68. Apotex has submitted ANDA No. 077-982 in order to obtain approval under the Federal Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a drug product the use of which is claimed in the '294 patent, before the expiration of the '294 patent. On information and belief, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

69. On information and belief, when Apotex filed ANDA No. 077-982 seeking approval to market alendronate sodium tablets before the expiration of the '294 patent, it was aware of the existence of the '294 patent and that the filing of ANDA No. 077-982 constituted an act of infringement of that patent.

70. On information and belief, Apotex acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '294 patent.

71. On information and belief, the infringement by Apotex of the '294 patent was and is willful.

72. On information and belief, as and to the extent Apotex has committed any infringing act with respect to alendronate other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), such infringement was willful.

REQUESTED RELIEF

Plaintiff Merck respectfully seeks the following relief:

a. That judgment be entered that Apotex has infringed the '941, '590, '726, '207, '410, '004, '329, '801, and '294 patents by submitting ANDA No. 077-982;

b. That a permanent injunction be issued under 35 U.S.C. § 271(e) restraining or enjoining Apotex, its officers, agents or attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any therapeutic composition, and/or method of use covered by the '941, '590, '726, '207, '410, '004, '329, '801, and '294 patents for the full term thereof, including the terms of other patents and the term of the pediatric exclusivity period listed in the Orange Book for Merck's 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg FOSAMAX® tablets, and from inducing or contributing to such activities;

c. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of ANDA No. 077-982 be a date which is not earlier than the last to expire of the asserted patents, including the terms of other patents and the term of the pediatric exclusivity period listed in the Orange Book for Merck's 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg FOSAMAX® tablets;

d. That judgment be entered that Defendant Apotex willfully and deliberately infringed the '941, '590, '726, '207, '410, '004, '329, '801, and '294 patents;

e. That this is an exceptional case under 35 U.S.C. § 285, and that judgment be entered for costs and reasonable attorneys fees to be awarded to Merck; and

f. That this Court award such other and further relief as the Court may deem proper under the circumstances.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Mary B. Graham

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Dated: April 7, 2006
515065

EXHIBIT 1

US005358941A

United States Patent [19]

Bechard et al.

[11] **Patent Number: 5,358,941**

[45] **Date of Patent: Oct. 25, 1994**

[54] **DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS WITH LACTOSE**

[75] Inventors: **Simon R. Bechard,** Laval, Canada; **Kenneth A. Kramer,** Green Lane; **Ashok V. Katdare,** Norristown, both of Pa.

[73] Assignee: **Merck & Co., Inc.,** Rahway, N.J.

[21] Appl. No.: **984,399**

[22] Filed: **Dec. 2, 1992**

[51] **Int. Cl.**[5] **A61K 31/66**

[52] **U.S. Cl.** **514/102;** 514/104; 514/960; 514/961

[58] **Field of Search** 514/959, 960, 12, 102, 514/141, 738, 786, 104; 424/479

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,942,157	7/1990	Gall et al.	514/108
5,041,428	8/1991	Isomura et al.	514/102
5,047,246	9/1991	Gallian et al.	424/464
5,070,108	12/1991	Margolis	514/725
5,158,944	10/1992	Makino et al.	514/167

FOREIGN PATENT DOCUMENTS

1036368 7/1986 United Kingdom .

OTHER PUBLICATIONS

Remington's Pharmaceuticals Science, 15th Edition Mack Pub. Co., Easton, Pa. pp. 1586–1588 (1978).

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Attorney, Agent, or Firm—Joanne M. Giesser; Melvin Winokur; Paul D. Matukaitis

[57] **ABSTRACT**

Pharmaceutical compositions of bisphosphonic acids, and salts thereof, are prepared by direct compression/dry mix tablet formulation. These pharmaceutical compositions are useful in the treatment of disturbances involving calcium or phosphate metabolism, in particular, the treatment and prevention of diseases involving bone resorption, especially osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease.

8 Claims, No Drawings

DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS WITH LACTOSE

BACKGROUND

The pharmaceutical industry employs various methods for compounding pharmaceutical agents in tablet formulations. In particular, wet granulation is one of the most prevalent methods.

A variety of bisphosphonic acids have been disclosed as being useful in the treatment and prevention of diseases involving bone resorption. Representative examples may be found in the following: U.S. Pat. No. 3,962,432; U.S. Pat. No. 4,054,598; U.S. Pat. No. 4,267,108; U.S. Pat. No. 4,327,039; U.S. Pat. No. 4,621,077; U.S. Pat. No. 4,624,947; U.S. Pat. No. 4,746,654; U.S. Pat. No. 4,922,077; and EPO Patent Pub. No. 0,252,504. Standard methods for tablet formulation of bisphosphonic acids, however, suffer serious difficulties.

In particular, bisphosphonic acids which bear a basic nitrogen-containing functionality may interact with the lactose of standard formulations resulting in discoloration, instability and potency loss. This degradation of the active ingredient is particularly pronounced in the presence of water and/or elevated temperature. It is speculated that this incompatibility is specifically due to the Maillard (or "browning") reaction in which the free amino group of the bisphosphonic acid reacts with the "glycosidic" hydroxyl group of a sugar (such as lactose) ultimately resulting in the formation of brown pigmented degradates. Although this problem may be avoided by the elimination of lactose, the use of lactose as an inert diluent is generally desirable.

The present invention solves this problem by providing a tablet formulation and process therefor that avoids such interaction between the bisphosphonic acid and the lactose in the formulation. In addition, the present invention also provides a processing advantage since it requires only blending of the ingredients without granulation or addition of water prior to compression.

DESCRIPTION OF THE INVENTION

The present invention is directed in a first embodiment to a process for the preparation of pharmaceutical compositions of bisphosphonic acids by direct compression (dry mix) tablet formulation. This process employs a blend of a bisphosphonic acid and minimal amounts of other processing aids with no water added. The tablet formulation is prepared by mixing the formulation ingredients with no hydration (i.e. no additional water is added to the mixture) prior to direct compression.

More specifically, this embodiment of the present invention concerns a process for the preparation of a tablet containing a bisphosphonic acid as an active ingredient which process comprises:

forming a mixture by mixing the active ingredient with:

a diluent,

a dry binder,

a disintegrant,

and optionally one or more additional ingredients selected from the group consisting of: compression aids, flavors, flavor enhancers, sweeteners and preservatives; lubricating the mixture with a lubricant; and compressing the resultant lubricated mixture into a desired tablet form.

The disclosed process may be used to prepare solid dosage forms, particularly tablets, for medicinal administration.

Preferred diluents include lactose. In particular, anydrous lactose is preferred from the flow processing point of view, although hydrous fast flow lactose may also be employed.

A preferred dry binder is cellulose. In particular, microcrystalline cellulose is preferred. Microcrystalline cellulose is available commercially under the trade name "Avicel" from FMC Corporation.

The disintegrant may be one of several modified starches or modified cellulose polymers, in particular, crosscarmellose sodium is preferred. Crosscarmellose sodium NF Type A is commercially available under the trade name "Ac-di-sol".

Preferred lubricants include magnesium stearate.

Examples of the bisphosphonic acids which may be employed as active ingredients in the instant invention include:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;

or a pharmaceutically acceptable salt thereof.

Methods for the preparation of bisphosphonic acids may be found in, e.g., U.S. Pat. No. 3,962,432; U.S. Pat. No. 4,954,598; U.S. Pat. No. 4,267,108; U.S. Pat. No. 4,327,039; U.S. Pat. No. 4,407,761; U.S. Pat. No. 4,621,077; U.S. Pat. No. 4,624,947; U.S. Pat. No. 4,746,654; U.S. Pat. No. 4,922,077; and EPO Patent Pub. No. 0,252,504. In particular, methods for the preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate may be found in U.S. Pat. No. 4,407,761 and U.S. Pat. No. 4,922,077, respectively.

The pharmaceutically acceptable salts of bisphosphonic acids may also be employed in the instant invention. Examples of base salts of bisphosphonic acids include ammonium salts, alkali metal salts such as potassium and sodium (including mono-, di- and tri-sodium) salts (which are preferred), alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. The non-toxic, physiologically acceptable salts are preferred. The salts may be prepared by methods known in the art, such as in U.S. Pat. No. 4,922,077.

In the present invention it is preferred that the bisphosphonic acid is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid. It is even more preferred that the bisphosphonic acid is a sodium salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, in particular, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

Another embodiment of the present invention is a direct compression pharmaceutical composition, such as a tablet, comprising a bisphosphonic acid, which is prepared by the disclosed process. In general, these pharmaceutical compositions comprise by weight, about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; and from about 60 to 99.5% by weight of processing aids with no water added. More specifically, the processing aids are a diluent, a dry binder, a disintegrant and a lubricant. Preferred processing aids include: anhydrous lactose or hydrous fast flow lactose; microcrystalline cellulose; croscarmallose sodium; and magnesium stearate.

Preferred pharmaceutical compositions comprise about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; about 10 to 80% by weight of anhydrous lactose or hydrous fast flow lactose; about 5 to 50% by weight of microcrystalline cellulose; about 0.5 to 10% by weight of croscarmallose sodium; and about 0.1 to 5% by weight of magnesium stearate.

The preferred pharmaceutical compositions are generally in the form of tablets. The tablets may be, for example, from 50 mg to 1.0 g in net weight, more preferably 100 to 500 mg net weight, and even more preferably 200 to 300 mg net weight.

More preferred pharmaceutical compositions in accordance with the present invention comprise: about 0.5 to 25% by weight of a bisphosphonic acid selected from 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 30 to 70% by weight of anhydrous lactose or hydrous fast flow lactose; about 30 to 50% by weight of microcrystalline cellulose; about 0.5 to 5% by weight of croscarmallose sodium; and about 0.1 to 2% by weight of magnesium stearate.

Especially preferred pharmaceutical compositions comprise about 1 to 25% of the active ingredient, about 40 to 60% by weight of anhydrous lactose; about 35 to 45% by weight of microcrystalline cellulose; about 0.5 to 2% by weight of croscarmallose sodium; and about 0.1 to 1% by weight of magnesium stearate. Preferred pharmaceutical compositions as envisioned for commercial development are as follows.

Tablets of 2.5 mg potency free acid:

about 1.63% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 56.87% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 5 mg potency free acid:

about 3.25% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 55.25% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 25 mg potency free acid:

about 16.4% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 42.1% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 50 mg potency free acid:

about 21.8% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 36.7% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

The pharmaceutical tablet compositions of the present invention may also contain one or more additional formulation ingredients may be selected from a wide variety of excipients known in the pharmaceutical formulation art. According to the desired properties of the tablet, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparing tablet compositions. Such ingredients include, but are not limited to, diluents, compression aids, disintegrants, lubricants, binders, flavors, flavor enhancers, sweetener and preservatives.

The term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes, whether coated or uncoated, Substances which may be used for coating include hydroxypropylmethylcellulose, hydroxypropylcellulose, titanium oxide, talc, sweeteners, and colorants.

The pharmaceutical compositions of the present invention are useful in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. These diseases can be divided into two categories:

1. Abnormal (ectopic) depositions of calcium salts, mostly calcium phosphate, pathological hardening of tissues and bone malformations.

2. Conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in bone augmentation. A reduction in bone resorption can aleviate the pain associated with osteolytic lesions and reduce the incidence and/or growth of those lesions.

These diseases include: osteoporosis (including estrogen defficiency, immobilization, glucocorticoid induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcimia, metastatic bone disease, peridontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany.

Increased bone resorption can be accompanied by pathologically high calcium and phosphate concentrations in the plasma, which would be aleviated by use of the instant pharmaceutical compositions.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

EXAMPLE 1

Procedure for Manufacturing 5 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	6.55 mg	26.2 g
Anhydrous Lactose, NF	110.45 mg	441.8 g
Microcrystaline Cellulose NF	80.0 mg	320.0 g
Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0 g

-continued

Ingredients	Per Tablet	Per 4,000 Tablets
Croscarmellose Sodium NF Type A	2.00 mg	8.0 g

The active ingredient (equivalent to 5 mg anhydrous free acid per tablet) was premixed with ⅓ of the microcrystaline cellulose NF and ½ of the anhydrous lactose NF in a ribbon blender for 5 minutes at 20 RPM. To the premix was added the remaining ⅔ of the microcrystaline cellulose NF and the remaining ½ of the anhydrous lactose NF. This was blended for 10 minutes at 20 RPM. Crosscarmellose sodium was added to the blended powders and mixed for 5 minutes at 20 RPM. Finally the magnesium stearate was added to the mixture by passing through a 90 mesh screen and blended for an additional 5 minutes at 20 RPM. The lubricated mixture was compressed to provide tablets of 5 mg active ingredient.

EXAMPLE 2

Procedure for Manufacturing 25 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	32.75 mg	131.0 g
Anhydrous Lactose, NF	84.25 mg	337.0 g
Microcrystaline Cellulose NF	80.0 mg	320.0 g
Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0 g
Croscarmellose Sodium NF Type A	2.00 mg	8.0 g

Tablets were prepared using essentially the procedure of Example 1.

EXAMPLE 3

Procedure for Manufacturing 50 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	65.5 mg	163.75 g
Anhydrous Lactose, NF	110.0 mg	275.0 g
Microcrystaline Cellulose NF	120.0 mg	300.0 g
Magnesium Stearate Impalpable Powder NF	1.5 mg	3.75 g
Croscarmellose Sodium NF Type A	3.0 mg	7.5 g

Tablets were prepared using essentially the procedure of Example 1.

EXAMPLE 4

Stability Studies

Tablet formulations of the active ingredient (equivalent to 5 mg anhydrous free 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid per tablet) were prepared under different conditions with differing excipients. The tablets were subjected to stability studies under open dish conditions at 40° C./75% relative humidity. The following observations were noted:

1. Tablet discoloration occured within 2 weeks in formulations which were manufactured by wet granulation and contained anhydrous lactose.

2. Tablet discoloration occured within 4 weeks in formulations which were manufactured by wet granulation and contained hydrous lactose.

3. There was no tablet discoloration after 4 weeks in formulations which manufactured as a direct compression (dry mix) formulation. Assay of the active ingredient confirmed that there was no loss of potency or formation of degradates over the same time period.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

What is claimed is:

1. A pharmaceutical composition comprising by weight, about 0.5 to 40% by weight of an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;

or a pharmaceutically acceptable salt thereof; and from about 60 to 99.5% by weight of excipients consisting essentially of:

anhydrous lactose; microcrystalline cellulose; croscarmallose sodium; and magnesium stearate.

2. A pharmaceutical composition comprising by weight, about 0,5 to 40% by weight of an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino>-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-<hydroxymethylene-1,1-bisphosphonic acid)-piperidine;

or a pharmaceutically acceptable salt thereof;

about 10 to 80% by weight of anhydrous lactose;

about 5 to 50% by weight of microcrystalline cellulose;

about 0.5 to 10% by weight of croscarmallose sodium; and

about 0.1 to 5% by weight of magnesium stearate.

3. The pharmaceutical composition of claim 2 comprising about 0.5 to 25% by weight of the active ingredient, about 30 to 70% by weight of anhydrous lactose; about 30 to 50% by weight of microcrystalline cellulose; about 0.5 to 5% by weight of croscarmallose sodium; and about 0.1 to 2% by weight of magnesium stearate.

4. The pharmaceutical composition of claim 2 wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

5. The pharmaceutical composition of claim 2 wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

6. The pharmaceutical composition of claim 5 comprising about 1 to 25% by weight of the active ingredient, 4-amino-1-hydroxybutylidene-1,1bisphosphonic acid monosodium salt trihydrate, about 40 to 60% by weight of anhydrous lactose; about 35 to 45% by weight of microcrystalline cellulose; about 0.5 to by weight of croscarmallose sodium; and about 0.1 to by weight of magnesium stearate.

7. The pharmaceutical composition of claim 5 in the form of a tablet.

8. The pharmaceutical composition of claim 2 in the form of a tablet.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,358,941

DATED : 10/25/94

INVENTOR(S) : SIMON R. BECHARD et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At Col. 6, Claim 2, line 49, "0,5" should read -- 0.5 --.

At Col. 6, Claim 2, line 59, "3-(N,N-dimethylamino>-1-hydroxypropylidene-1,1-" should read -- 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1- --.

At Col. 6, Claim 2, line 65, "4-<hydroxymethylene-1,1-bisphosphonic acid)-" should read -- 4-(hydroxymethylene-1,1-bisphosphonic acid)- --.

At Col. 8, Claim 6, line 10, "weight of microcrystalline cellulose; about 0.5 to by" should read -- weight of microcrystalline cellulose; about 0.5 to 2% by --.

At Col. 8, Claim 6, line 11, "weight of croscarmallose sodium; and about 0.1 to by" should read -- weight of croscarmallose sodium; and about 0.1 to 1% by --.

Signed and Sealed this

Eleventh Day of January, 2000

Attest:

Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

EXHIBIT 2

US005681590A

United States Patent [19]

Bechard et al.

[11] **Patent Number: 5,681,590**

[45] **Date of Patent: *Oct. 28, 1997**

[54] **DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS**

[75] Inventors: **Simon R. Bechard**, Quebec, Canada; **Kenneth A. Kramer**, Green Lane; **Ashok V. Katdare**, Norristown, both of Pa.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,358,941.

[21] Appl. No.: **454,100**

[22] PCT Filed: **Nov. 17, 1993**

[86] PCT No.: **PCT/US93/11172**

§ 371 Date: **Jul. 26, 1995**

§ 102(e) Date: **Jul. 26, 1995**

[87] PCT Pub. No.: **WO94/12200**

PCT Pub. Date: **Jun. 9, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 984,399, Dec. 2, 1992, Pat. No. 5,358,941.

[51] **Int. Cl.**^{6} **A61K 9/20**

[52] **U.S. Cl.** **424/464**; 424/465

[58] **Field of Search** 424/464, 465

[56] **References Cited**

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Primary Examiner—Amy Hulina
Attorney, Agent, or Firm—Joanne M. Giesser; Melvin Winokur

[57] **ABSTRACT**

Pharmaceutical compositions of bisphosphonic acids, and salts thereof, are prepared by direct compression/dry mix tablet formulation. These pharmaceutical compositions are useful in the treatment of disturbances involving calcium or phosphate metabolism, in particular, the treatment and prevention of diseases involving bone resorption, especially osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease.

17 Claims, No Drawings

DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS

This application is the U.S. National Phase Application of International patent application Ser. No. PCT/US93/11172, filed Nov. 17, 1993, which is a continuation of U.S. patent application Ser. No. 984,399, filed Dec. 2, 1992, now U.S. Pat. No. 5,358,941, issued Oct. 25, 1994.

BACKGROUND OF THE INVENTION

The pharmaceutical industry employs various methods for compounding pharmaceutical agents in tablet formulations. In particular, wet granulation is one of the most prevalent methods.

A variety of bisphosphonic acids have been disclosed as being useful in the treatment and prevention of diseases involving bone resorption. Representative examples may be found in the following: U.S. Pat. No. 3,962,432; U.S. Pat. No. 4,054,598; U.S. Pat. No. 4,267,108; U.S. Pat. No. 4,327,039; U.S. Pat. No. 4,621,077; U.S. Pat. No. 4,624,947; U.S. Pat. No. 4,746,654; U.S. Pat. No. 4,922,077; and EPO Patent Pub. No. 0,252,504. Standard methods for tablet formulation of bisphosphonic acids, however, suffer serious difficulties.

In particular, bisphosphonic acids which bear a basic nitrogen-containing functionality may interact with the lactose of standard formulations resulting in discoloration, instability and potency loss. This degradation of the active ingredient is particularly pronounced in the presence of water and/or elevated temperature. It is speculated that this incompatibility is specifically due to the Maillard (or "browning") reaction in which the free amino group of the bisphosphonic acid reacts with the "glycosidic" hydroxyl group of a sugar (such as lactose) ultimately resulting in the formation of brown pigmented degradates. Although this problem may be avoided by the elimination of lactose, the use of lactose as an inert diluent is generally desirable.

The present invention solves this problem by providing a tablet formulation and process therefor that avoids such interaction between the bisphosphonic acid and the lactose in the formulation. In addition, the present invention also provides a processing advantage since it requires only blending of the ingredients without granulation or addition of water prior to compression.

DESCRIPTION OF THE INVENTION

The present invention is directed in a first embodiment to a process for the preparation of pharmaceutical compositions of bisphosphonic acids by direct compression (dry mix) tablet formulation. This process employs a blend of a bisphosphonic acid and minimal amounts of other processing aids with no water added. The tablet formulation is prepared by mixing the formulation ingredients with no hydration (i.e. no additional water is added to the mixture) prior to direct compression.

More specifically, this embodiment of the present invention concerns a process for the preparation of a tablet containing a bisphosphonic acid as an active ingredient which process comprises:

forming a mixture by mixing the active ingredient with:
- a diluent,
- a dry binder,
- a disintegrant,
- and optionally one or more additional ingredients selected from the group consisting of: compression aids, flavors, flavor enhancers, sweeteners and preservatives;

lubricating the mixture with a lubricant; and compressing the resultant lubricated mixture into a desired tablet form.

The disclosed process may be used to prepare solid dosage forms, particularly tablets, for medicinal administration.

Preferred diluents include lactose. In particular, anydrous lactose is preferred from the flow processing point of view, although hydrous fast flow lactose may also be employed.

A preferred dry binder is cellulose. In particular, microcrystalline cellulose is preferred. Microcrystalline cellulose is available commercially under the trade name "Avicel" from FMC Corporation.

The disintegrant may be one of several modified starches or modified cellulose polymers, in particular, crosscarmellose sodium is preferred. Crosscarmellose sodium NF Type A is commercially available under the trade name "Ac-di-sol".

Preferred lubricants include magnesium stearate.

Examples of the bisphosphonic acids which may be employed as active ingredients in the instant invention include:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;

or a pharmaceutically acceptable salt thereof.

Methods for the preparation of bisphosphonic acids may be found in, e.g., U.S. Pat. No. 3,962,432; U.S. Pat. No. 4,054,598; U.S. Pat. No. 4,267,108; U.S. Pat. No. 4,327,039; U.S. Pat. No. 4,407,761; U.S. Pat. No. 4,621,077; U.S. Pat. No. 4,624,947; U.S. Pat. No. 4,746,654; U.S. Pat. No. 4,922,077; and EPO Patent Pub. No. 0,252,504. In particular, methods for the preparation of 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate may be found in U.S. Pat. No. 4,407,761 and U..S. Pat. No. 4,922,077, respectively.

The pharmaceutically acceptable salts of bisphosphonic acids may also be employed in the instant invention. Examples of base salts of bisphosphonic acids include ammonium salts, alkali metal salts such as potassium and sodium (including mono-, di- and tri-sodium) salts (which are preferred), alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. The non-toxic, physiologically acceptable salts are preferred. The salts may be prepared by methods known in the art, such as in U.S. Pat. No. 4,922,077.

In the present invention it is preferred that the bisphosphonic acid is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid. It is even more preferred that the bisphosphonic acid is a sodium salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, in particular, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

Another embodiment of the present invention is a direct compression pharmaceutical composition, such as a tablet, comprising a bisphosphonic acid, which is prepared by the disclosed process. In general, these pharmaceutical compositions comprise by weight, about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; and from about 60 to 99.5% by weight of processing aids with no water added. More specifically, the processing aids are a diluent, a dry binder, a disintegrant and a lubricant. Preferred processing aids include: anhydrous lactose or hydrous fast flow lactose; microcrystalline cellulose; croscarmallose sodium; and magnesium stearate.

Preferred pharmaceutical compositions comprise about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; about 10 to 80% by weight of anhydrous lactose or hydrous fast flow lactose; about 5 to 50% by weight of microcrystalline cellulose; about 0.5 to 10% by weight of croscarmallose sodium; and about 0.1 to 5% by weight of magnesium stearate.

The prefected pharmaceutical compositions are generally in the form of tablets. The tablets may be, for example, from 50 mg to 1.0 g in net weight, more preferably 100 to 500 mg net weight, and even more preferably 200 to 300 mg net weight.

More preferred pharmaceutical compositions in accordance with the present invention comprise: about 0.5 to 25% by weight of a bisphosphonic acid selected from 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 30 to 70% by weight of anhydrous lactose or hydrous fast flow lactose; about 30 to 50% by weight of microcrystalline cellulose; about 0.5 to 5% by weight of croscarmallose sodium; and about 0.1 to 2% by weight of magnesium stearate.

Especially preferred pharmaceutical compositions comprise about 1 to 25% of the active ingredient, about 40 to 60% by weight of anhydrous lactose; about 35 to 45% by weight of microcrystalline cellulose; about 0.5 to 2% by weight of croscarmallose sodium; and about 0.1 to 1% by weight of magnesium stearate. Preferred pharmaceutical compositions as envisioned for commercial development are as follows.

Tablets of 2.5 mg potency free acid:

about 1.63% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 56.87% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmailose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 5 mg potency free acid:

about 3.25% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 55.25% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 25 mg potency free acid:

about 16.4% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 42.1% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 50 mg potency free acid:

about 21.8% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 36.7% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

The pharmaceutical tablet compositions of the present invention may also contain one or more additional formulation ingredients may be selected from a wide variety of excipients known in the pharmaceutical formulation art. According to the desired properties of the tablet, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparing tablet compositions. Such ingredients include, but are not limited to, diluents, compression aids, disintegrants, lubricants, binders, flavors, flavor enhancers, sweetenter and preservatives.

The term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes, whether coated or uncoated. Substances which may be used for coating include hydroxypropylmethylcellulose, hydroxypropylcellulose, titanium oxide, talc, sweeteners, and colorants.

The pharmaceutical compositions of the present invention are useful in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. These diseases can be divided into two categories:

1. Abnormal (ectopic) depositions of calcium salts, mostly calcium phosphate, pathological hardening of tissues and bone malformations.
2. Conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in bone augmentation. A reduction in bone resorption can aleviate the pain associated with osteolytic lesions and reduce the incidence and/or growth of those lesions.

These diseases include: osteoporosis (including estrogen defficiency, immobilization, glucocorticoid induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcimia, metastatic bone disease, peridontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany.

Increased bone resorption can be accompanied by pathologically high calcium and phosphate concentrations in the plasma, which would be aleviated by use of the instant pharmaceutical compositons.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

EXAMPLE 1

Procedure for Manufacturing 5 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	6.55 mg	26.2 g
Anhydrous Lactose, NF	110.45 mg	441.8 g
Microcrystaline Cellulose NF	80.0 mg	320.0 g
Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0 g
Croscarmellose Sodium NF Type A	2.00 mg	8.0 g

The active ingredient (equivalent to 5 mg anhydrous free acid per tablet) was premixed with ⅓ of the microcrystaline

cellulose NF and ½ of the anhydrous lactose NF in a ribbon blender for 5 minutes at 20 RPM. To the premix was added the remaining ⅔ of the microcrystaline cellulose NF and the remaining ½ of the anhydrous lactose NF. This was blended for 10 minutes at 20 RPM. Crosscarmellose sodium was added to the blended powders and mixed for 5 minutes at 20 RPM. Finally the magnesium stearate was added to the mixture by passing through a 90 mesh screen and blended for an additional 5 minutes at 20 RPM. The lubricated mixture was compressed to provide tablets of 5 mg active ingredient.

EXAMPLE 2

Procedure for Manufacturing 2.5 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet
Active ingredient (monosodium salt trihydrate)	3.26 mg
Anhydrous Lactose, NF	113.74 mg
Microcrystaline Cellulose NF	80.0 mg
Magnesium Stearate Impalpable Powder NF	1.00 mg
Croscarmellose Sodium NF Type A	2.00 mg

Tablets were prepared using the procedure of Example 1.

EXAMPLE 3

Procedure for Manufacturing 10.0 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet
Active ingredient (monosodium salt trihydrate)	13.05 mg
Anhydrous Lactose, NF	103.95 mg
Microcrystaline Cellulose NF	80.0 mg
Magnesium Stearate Impalpable Powder NF	1.00 mg
Croscarmellose Sodium NF Type A	2.00 mg

Tablest were prepared using the procedure of Example 1.

EXAMPLE 4

Procedure for Manufacturing 40.0 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet
Active ingredient (monosodium salt trihydrate)	51.21 mg
Anhydrous Lactose, NF	64.79 mg
Microcrystaline Cellulose NF	80.0 mg
Magnesium Stearate Impalpable Powder NF	1.00 mg
Croscarmellose Sodium NF Type A	2.00 mg

Tablets were prepared using the procedure of Example 1.

EXAMPLE 5

Procedure for Manufacturing 25 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	32.75 mg	131.0 g
Anhydrous Lactose, NF	84.25 mg	337.0 g
Microcrystaline Cellulose NF	80.0 mg	320.0 g
Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0 g
Croscarmellose Sodium NF Type A	2.00 mg	8.0 g

Tablets were prepared using the procedure of Example 1.

EXAMPLE 6

Procedure for Manufacturing 50 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 2,500 Tablets
Active ingredient (monosodium salt trihydrate)	65.5 mg	163.75 g
Anhydrous Lactose, NF	110.45 mg	275.0 g
Microcrystaline Cellulose NF	120.0 mg	300.0 g
Magnesium Stearate Impalpable Powder NF	1.00 mg	3.75 g
Croscarmellose Sodium NF Type A	2.00 mg	7.5 g

Tablets were prepared using the procedure of Example 1.

EXAMPLE 7

Stability Studies

Tablet formulations of the active ingredient (equivalent to 5 mg anhydrous free 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid per tablet) were prepared under different conditions with differing excipients. The direct compression tablets were prepared according to the procedure of Example 1 and the wet granulated tablets were prepared according to the procedure below. The tablets were subjected to stability studies under open dish conditions at 40° C./75% relative humidity. The following observations were noted:

1. Tablet discoloration occured within 2 weeks in formulations which were manufactured by wet granulation and contained anhydrous lactose.
2. Tablet discoloration occured within 4 weeks in formulations which were manufactured by wet granulation and contained hydrous lactose.
3. There was no tablet discoloration after 4 weeks in formulations which manufactured as a direct compression (dry mix) formulation. Assay of the active ingredient confirmed that there was no loss of potency or formation of degradates over the same time period. Table I demonstrates the stability characteristics of the direct compression formulation as compared to a wet granulated formulation.

TABLE I

Three-Month Data of 5 mg Probe Stability Lots

(a). Direct Compression

	Assay, % initial			
	Open Dish		HDPE/CRC Bottle	
Condition	cpd	Adduct	MK-0217	Adduct
40° C.	101.2%	—	99.8%	—
40° C/75% RH	102.9%	—	98.5%	—
			100.9%*	—
60° C.	100.6%	—	101.3%	—
RT/90% RH	103.5%	—	102.1%	—

(b). Wet Granulation

	Assay, % initial			
	Open Dish		HDPE/CRC Bottle	
Condition	epd	Adduct	MK-0217	Adduct
40° C.	99.7%	—	97.0%	—
			100.0%**	—
40° C./75% RH	84.1%	15.9%	94.6%	5.6%
			99.7%**	—
60° C.	92.6%	trace***	94.3%	trace***
			94.6%**	trace
RT/90% RH	101.4%	—	100.4%	—
			99.4%	—

*Duplicate value
**With desiccant
***Trace indicates that the adduct peak is detectable (~5%) but not quantifiable under experimental conditions.
cpd = 4-amino-1-hydroxybutylidene-1,1-bispbosphonic acid

Process for wet granulation tablets

1) Anhydrous lactose, alendronate sodium and microcrystalline cellulose was mixed in a suitable size blender.
2) The blend was strained through mesh #30 followed by remixing for an additional time.
3) The powder mixture was granulated with an adequate quantity of water until caking occurred.
4) The wet mass was poured through a screen #5.
5) The wet sized granulation was dried in a forced air dryer at 40°–50° C. until the loss on drying was less then 2% at 105° C.
6) The dry granulation was sized through a suitable screen.
7) The drysized granulation was mixed with croscarmellose sodium followed by magnesium stearate.
8) Tablets were compressed using the labeled granulation.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

What is claimed is:

1. A process for the preparation of a tablet containing an active ingredient selected from:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid;

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;

or a pharmaceutically acceptable salts thereof;

which process comprises:

forming a mixture by mixing the active ingredient with:

a diluent, selected from: anhydrous lactose and hydrous fast

flow lactose,

a dry binder,

a disintegrant,

and optionally one or more additional ingredients selected

from the group consisting of: compression aids, flavors, flavor enhancers, sweeteners and preservatives;

lubricating the mixture with a lubricant; and

compressing the resultant lubricated mixture into a desired

tablet form.

2. The process of claim 1 wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

3. The process of claim 1 wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

4. The process of claim 1 wherein the dry binder is microcrystalline cellulose.

5. The process of claim 1 wherein the disintegrant is selected from the group consisting of modified starch, modified cellulose polymer, and croscarmallose sodium, and a combination thereof.

6. The process of claim 1 wherein the disintegrant is croscarmallose sodium.

7. The process of claim 1 wherein the lubricant is magnesium stearate.

8. A solid dosage form containing an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;

or a pharmaceutically acceptable salt thereof;

wherein the dosage form is prepared by the process of claim 1.

9. A pharmaceutical composition comprising by weight, about 0.5 to 40% by weight of an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;

or a pharmaceutically acceptable salt thereof;

and from about 60 to 99.5% by weight of excipients consisting essentially of: hydrous fast flow lactose; microcrystalline cellulose; croscarmallose sodium; and magnesium stearate.

10. A pharmaceutical composition comprising by weight, about 0.5 to 40% by weight of an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;

or a pharmaceutically acceptable salt thereof;

about 10 to 80% by weight of hydrous fast flow lactose; about 5 to 50% by weight of microcrystalline cellulose; about 0.5 to 10% by weight of croscarmallose sodium; and about 0.1 to 5% by weight of magnesium stearate.

11. The pharmaceutical composition of claim **10** comprising about 0.5 to 25% by weight of the active ingredient, about 30% to 70% by weight of hydrous fast flow lactose; about 30 to 50% by weight of microcrystalline cellulose; about 0.5 to 5% by weight of croscarmallose sodium; and about 0.1 to 2% by weight of magnesium stearate.

12. The pharmaceutical composition of claim **10** wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

13. The pharmaceutical composition of claim **10** wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

14. A tablet prepared from the pharmaceutical composition of claim **13**.

15. A tablet prepared from the pharmaceutical composition of claim **10**.

16. A process for the preparation of a table containing as active ingredient a basic nitrogen containing bisphosphonate: which process comprises:

forming a mixture by mixing the active ingredient with:

a diluent, selected from: anhydrous lactose or hydrous fast flow lactose,

a dry binder,

a disintegrant,

and optionally one or more additional ingredients selected

from the group consisting of: compression aids, flavors, flavor enhancers, sweeteners and preservatives;

lubricating the mixture with a lubricant; and

compressing the resultant lubricated mixture into a desired tablet form.

17. A solid dosage form containing as active ingredient a basic nitrogen containing bisphosphonate wherein the dosage form is prepared by the process of claim **1**.

* * * * *

EXHIBIT 3

US005849726A

United States Patent [19]

Brenner et al.

[11] **Patent Number: 5,849,726**

[45] **Date of Patent: Dec. 15, 1998**

[54] **ANHYDROUS ALENDRONATE MONOSODIUM SALT FORMULATIONS**

[75] Inventors: **Gerald S. Brenner**, Norristown; **Drazen Ostovic**, Lansdale; **Earl R. Oberholtzer, Jr.**, Hatfield, all of Pa.; **J. Eric Thies**, Scotch Plains, N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **973,386**

[22] PCT Filed: **Jun. 3, 1996**

[86] PCT No.: **PCT/US96/08284**

§ 371 Date: **Dec. 3, 1997**

§ 102(e) Date: **Dec. 3, 1997**

[87] PCT Pub. No.: **WO96/39149**

PCT Pub. Date: **Dec. 12, 1996**

Related U.S. Application Data

[63] Continuation of Ser. No. 469,143, Jun. 6, 1995, abandoned.

[51] **Int. Cl.**[6] **A61K 31/66**

[52] **U.S. Cl.** **514/108**

[58] **Field of Search** 514/108

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,621,077	11/1986	Rosini et al.	514/108
4,922,007	5/1990	Kieczykowski et al.	562/13
5,019,651	5/1991	Kieczykowski	562/13

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Anthony D. Sabatelli; Melvin Minokur

[57] **ABSTRACT**

Disclosed is a method for treating and preventing bone loss in patients by administering a formulation of anhydrous alendronate sodium. Also described is a pharmaceutical dosage form of said anhydrous alendronate sodium, being anhydrous **4**-amino-**1**-hydroxy-butylidene-**1**,**1**-bisphosphonic acid, monosodium salt, in a pharmaceutically acceptable excipient.

7 Claims, No Drawings

ANHYDROUS ALENDRONATE MONOSODIUM SALT FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This is a U.S. National Phase Application of International Patent Application No. PCT/US96/08284, filed Jun. 3, 1996, which is a continuation of U.S. patent application Ser. No., 08/469,143, filed Jun. 6, 1995, now abandoned.

FIELD OF THE INVENTION

The instant invention relates to the use of the anhydrous crystal form of alendronate sodium, i.e., 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium, hereinafter referred to as "anhydrous alendronate sodium" or "AAS", to inhibit bone resorption in human patients.

BACKGROUND OF THE INVENTION

Normal bones are living tissues undergoing constant resorption and redeposition of calcium, with the net effect of maintenance of a constant mineral balance. The dual process is commonly called "bone turnover". In normal growing bones, the mineral deposition is in equilibrium with the mineral resorption, whereas in certain pathological conditions, bone resorption exceeds bone deposition, for instance due to malignancy or primary hyperparathyroidism, or in osteoporosis. In other pathological conditions the calcium deposition may take place in undesirable amounts and areas leading to e.g., heterotopic calcification, osteoarthritis, kidney or bladder stones, atherosclerosis, and Paget's disease which is a combination of an abnormal high bone resorption followed by an abnormal calcium deposition.

U.S. Pat. No. 4,621,077 to Istituto Gentili discloses a method of treating urolithiasis and inhibiting bone reabsorption by the use of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (also named 4-amino-1-hydroxybutane-1,1-bisphosphonic acid) and its salts with an alkali metal, an organic base or a basic amino acid. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is described as being between 100 and 300 times more active than dichloromethane-biphosphonic acid in inhibiting bone reabsorption.

Alendronate sodium, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate, is an agent for combating bone resorption in bone diseases including osteoporosis and is described as a composition, method of use and synthesis along with other pharmaceutically acceptable salts in U.S. Pat. Nos. 4,922,007 and 5,019,651 (both assigned to Merck).

However, new crystalline forms of alendronate sodium are constantly being searched for to enable ease of formulation and better pharmacokinetics, e.g., desirable crystal habit, good flow properties, higher solubility, longer duration or quicker onset of action, and improved bioavailability. Particularly what is desired is a new formulation to overcome the gastric irritability associated with the administration of the free acid form of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid. This is of particular importance in cases where the patient has a history of gastrointestinal problems prior to recommended alendronate therapy.

SUMMARY OF THE INVENTION

The present invention provides a method for treating and/or preventing bone loss in a subject by the administering

to said patient a pharmaceutically effective amount of the anhydrous form of alendronate sodium, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt. Because the aqueous pH of the monosodium salt is about 4.4, as compared to the free acid which is about 2.6, there is substantially less gastric irritability associated with the administration of the anhydrous monosodium salt to a human patient.

Also provided is a pharmaceutical composition comprising a pharmaceutically effective amount of anhydrous alendronate sodium, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt, in a pharmaceutically acceptable excipient mixture.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The method disclosed herein can be used to treat humans, particularly females who are post-menopausal, with an osteogenically effective amount of anhydrous alendronate sodium to inhibit bone resorption in need of such treatment. Such need arises locally in cases of bone fracture, non-union, defect, and the like. Such need also arises in cases of systemic bone disease, as in osteoporosis, osteoarthritis, Paget's disease, osteomalacia, multiple myeloma and other forms of cancer, steroid therapy, and age-related loss of bone mass.

The term "inhibition of bone resorption" as used herein, refers to treatment and prevention of bone loss, especially inhibiting the removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity. Thus, the term "inhibitor of bone resorption" as used herein refers to agents that prevent bone loss by the direct or indirect alteration of osteoclast formation or activity and which may increase bone mass in patient treatment populations.

The term "osteogenically effective" as used herein, means that amount which effects the turnover of mature bone. As used herein, an osteogenically effective dose is also "pharmaceutically effective."

The term "treatment" or "treating" as used herein shall mean (1) providing a subject with an amount of anhydrous alendronate sodium sufficient to act prophylactically to prevent the development of a weakened and/or unhealthy state; and/or (2) providing a subject with a sufficient amount of anhydrous alendronate sodium so as to alleviate or eliminate a disease state and/or the symptoms of a disease state, and a weakened and/or unhealthy state.

Pharmaceutical formulations of the invention which include anhydrous alendronate sodium for administration will generally include an osteogenically effective amount of anhydrous alendronate sodium to promote bone growth, in addition to a pharmaceutically acceptable excipient.

The precise therapeutic dosage of anhydrous alendronate sodium will vary with the age, size, sex and condition of the subject, the nature and severity of the disorder to be treated, and the like; thus, a precise effective amount cannot be specified in advance and will be determined by the caregiver. However, appropriate amounts may be determined by routine experimentation with animal models, as described below. In general terms, an effective dose for alendronate disodium is about 0.01 to 1 mg/kg per day of body weight. Particularly useful dosages are 2.72, 5.44, 10.88 and 43.52 mg per day/per person of anhydrous alendronate monosodium (equivalent to 2.5, 5.0, 10 and 40 mg free acid equivalents) per day per person.

The pharmaceutical composition described herein contains anhydrous alendronate monosodium salt in an amount of about 0.005 to 1.0 gram per gram of composition.

The pharmaceutical compositions according to the present invention containing anhydrous alendronate sodium may be prepared for use in the form of capsules or tablets for oral administration or for systemic use. The compositions are advantageously prepared together with inert carriers such as sugars (saccharose, glucose, lactose), starch and derivatives, cellulose and derivatives, gums, fatty acids and their salts, polyalcohols, talc, aromatic esters, and the like.

The composition can also be prepared by direct compression of a dry mix formulation as described in U.S. Pat. No. 5,358,941 (assigned to Merck & Co. Inc.). Particularly useful diluents in this composition are anhydrous lactose and microcrystalline cellulose.

Some typical pharmaceutical formulations (200 mg oral tablets) containing anhydrous alendronate sodium are shown below:

TABLETS (WHITE), 200 MG

	COMPOSITION IN MG/TABLET			
INGREDIENT	2.5 mg**	5.0 mg**	10.0 mg**	40.0 mg**
AAS*	2.72	5.44	10.88	43.52
Lactose Anhydrous NF	114.28	111.55	106.12	73.48
Microcrystalline Cellulose NF (Avicel PH 102)	80.0	80.0	80.0	80.0
Magnesium Stearate NF	1.00	1.00	1.00	1.00
Croscarmellose Sodium NF (Ac-Di-Sol)	2.00	2.00	2.00	2.00
Total	200	200	200	200

*AAS, anhydrous alendronate monosodium salt-active ingredient.
**Anhydrous alendronate free acid equivalent, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.
Note: The amounts of inactive ingredients may vary ± 10%

The methods and compositions of the invention are useful for treating bone fractures, defects and disorders which result from the pathological conditions of osteoporosis, osteoarthritis, Paget's disease, osteohalisteresis, osteomalacia, bone loss resulting from multiple myeloma other forms of cancer, bone loss resulting from side effects of disuse, other medical treatment (such as steroids), rheumatoid-related and age-related loss of bone mass.

The composition of the instant invention is also useful in lessening the risk of vertebral and non-vertebral fractures in osteoporotic post-menopausal women.

The composition described herein is also useful for the prevention and treatment of periodontal disease (see U.S. Pat. No. 5,270,365); to prevent or treat loosening of orthopedic implant devices; and, to lessen the risk in osteoporotic women of vertebral fractures, which composition can be administered in a protocol over a three year period.

The composition can also be used in combination with prostaglandins (see WO 94/06750), estrogen (see WO 94/14455), or growth hormone secretagogues to treat osteoporosis and the above-described conditions associated with abnormalities in bone resorption.

The following Example is given to illustrate the carrying out of the invention as contemplated by the inventors and should not be construed as being a limitation on the scope and spirit of the invention.

Example

Preparation of 4-Amino-1-Hydroxy-Butylidene-1,1-Bisphosphonic Acid Monosodium Salt Anhydrate

To a suspension of 4-amino-1-hydroxy-1,1-diphosphonic acid (4.02 g) in 150 ml of distilled water was added with stirring aqueous sodium hydroxide (0.5N) until the pH of the solution was 4.40. The stirred solution was triturated with 200 ml ethanol (absolute) to give a suspension of a fine white solid which was chilled at 5 degrees C. overnight. The obtained solid was collected by vacuum filtration, air dried, and then dried in vacuo at 100 degrees C. at 0.2 torr for 18 hours over P_2O_5 to yield 3.38 g, (91%) yield of the titled compound. A sample was submitted for CHN analysis;

For $C_4H_{12}NO_7P_2Na$: Anal.: C, 17.72; H, 4.46; N, 5.16 Found: C, 17.56; H, 4.67; N, 5.15 Melting Point of the solid was 244–245 degrees C.(d.)

The obtained titled salt displays a unique X-ray diffraction pattern.

Solubility of the anhydrous monosodium salt in water is about 300 mg/ml as compared to the free acid which is 8 mg/ml. However, above 40 mg/ml, the trihydrate precipitates out of the aqueous solution.

The solution pH of the monosodium salt at 40 mg/ml. is 4.4, as compared to the free acid which is pH 2.2 at 8 mg/ml.

The water adsorption by the anhydrous salt at lower humidities is quite slow.

What is claimed is:

1. A pharmaceutical composition comprising a pharmaceutically effective amount of anhydrous 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt in a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim **1** wherein said anhydrous 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt is present in the amount of 0.005 to 1.0 gram per gram of composition.

3. A method for treating and/or preventing bone loss in a subject, comprising administering to said subject in need thereof, the pharmaceutical composition as defined in claim **1**.

4. The method of claim **3**, wherein said subject is human.

5. The method of claim **3**, wherein the bone loss is osteoporosis-related, due to disuse, age-related, related to steroid therapy, rheumatoid-related, related to Paget's disease, or related to cancer.

6. The method of claim **3**, wherein the treatment is prophylactic.

7. The anhydrous form of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt.

* * * * *

EXHIBIT 4

US006008207A

United States Patent [19]

Brenner et al.

[11] Patent Number: 6,008,207

[45] Date of Patent: *Dec. 28, 1999

[54] **ANHYDROUS ALENDRONATE MONOSODIUM SALT FORMULATIONS**

[75] Inventors: **Gerald S. Brenner**, Norristown; **Drazen Ostovic**, Lansdale; **Earl R. Oberholtzer, Jr.**, Hatfield, all of Pa.; **J. Eric Thies**, Scotch Plains, N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/133,200**

[22] Filed: **Aug. 13, 1998**

Related U.S. Application Data

[63] Continuation of application No. 08/973,386, filed as application No. PCT/US96/08284, Jun. 3, 1996, which is a continuation of application No. 08/469,143, Jun. 6, 1995, abandoned.

[51] **Int. Cl.**[6] **A61K 31/66**

[52] **U.S. Cl.** **514/108**

[58] **Field of Search** 562/13; 514/108

[56] **References Cited**

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5,849,726	12/1998	Brenner et al.	514/108

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WO 95/08331	3/1995	WIPO .
WO 96/39107	12/1996	WIPO .

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Anthony D. Sabatelli; Melvin Winokur

[57] **ABSTRACT**

Disclosed is a method for treating and preventing bone loss in patients by administering a formulation of anhydrous alendronate sodium. Also described is a pharmaceutical doage form of said anhydrous alendronate sodium, being anhydrous 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid, monosodium salt, in a pharmaceutically acceptable excipient.

4 Claims, No Drawings

ANHYDROUS ALENDRONATE MONOSODIUM SALT FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation of application Ser. No. 08/973,387, filed Dec. 3, 1997, now U.S. Pat. No. 5,849,726 which in turn is the U.S. National phase application under 35 U.S.C. §371 of PCT application Ser. No. PCT/US96/08284, filed Jun. 3, 1996, which is a continuation of Ser. No. 08/469,143, filed Jun. 6, 1995, now abandoned.

FIELD OF THE INVENTION

The instant invention relates to the use of the anhydrous crystal form of alendronate sodium, i.e., 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium, hereinafter referred to as "anhydrous alendronate sodium" or "AAS", to inhibit bone resorption in human patients.

BACKGROUND OF THE INVENTION

Normal bones are living tissues undergoing constant resorption and redeposition of calcium, with the net effect of maintenance of a constant mineral balance. The dual process is commonly called "bone turnover". In normal growing bones, the mineral deposition is in equilibrium with the mineral resorption, whereas in certain pathological conditions, bone resorption exceeds bone deposition, for instance due to malignancy or primary hyperparathyroidism, or in osteoporosis. In other pathological conditions the calcium deposition may take place in undesirable amounts and areas leading to e.g., heterotopic calcification, osteoarthritis, kidney or bladder stones, atherosclerosis, and Paget's disease which is a combination of an abnormal high bone resorption followed by an abnormal calcium deposition.

U.S. Pat. No. 4,621,077 to Istituto Gentili discloses a method of treating urolithiasis and inhibiting bone reabsorption by the use of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (also named 4-amino-1-hydroxybutane-1,1-bisphosphonic acid) and its salts with an alkali metal, an organic base or a basic amino acid. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is described as being between 100 and 300 times more active than dichloromethane-biphosphonic acid in inhibiting bone reabsorption.

Alendronate sodium, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate, is an agent for combating bone resorption in bone diseases including osteoporosis and is described as a composition, method of use and synthesis along with other pharmaceutically acceptable salts in U.S. Pat. Nos. 4,922,007 and 5,019,651 (both assigned to Merck).

However, new crystalline forms of alendronate sodium are constantly being searched for to enable ease of formulation and better pharmacokinetics, e.g., desirable crystal habit, good flow properties, higher solubility, longer duration or quicker onset of action, and improved bioavailability. Particularly what is desired is a new formulation to overcome the gastric irritability associated with the administration of the free acid form of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid. This is of particular importance in cases where the patient has a history of gastrointestinal problems prior to recommended alendronate therapy.

SUMMARY OF THE INVENTION

The present invention provides a method for treating and/or preventing bone loss in a subject by the administering

to said patient a pharmaceutically effective amount of the anhydrous form of alendronate sodium, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt. Because the aqueous pH of the monosodium salt is about 4.4, as compared to the free acid which is about 2.6, there is substantially less gastric irritability associated with the administration of the anhydrous monosodium salt to a human patient.

Also provided is a pharmaceutical composition comprising a pharmaceutically effective amount of anhydrous alendronate sodium, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt, in a pharmaceutically acceptable excipient mixture.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The method disclosed herein can be used to treat humans, particularly females who are post-menopausal, with an osteogenically effective amount of anhydrous alendronate sodium to inhibit bone resorption in need of such treatment. Such need arises locally in cases of bone fracture, non-union, defect, and the like. Such need also arises in cases of systemic bone disease, as in osteoporosis, osteoarthritis, Paget's disease, osteomalacia, multiple myeloma and other forms of cancer, steroid therapy, and age-related loss of bone mass.

The term "inhibition of bone resorption" as used herein, refers to treatment and prevention of bone loss, especially inhibiting the removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity. Thus, the term "inhibitor of bone resorption" as used herein refers to agents that prevent bone loss by the direct or indirect alteration of osteoclast formation or activity and which may increase bone mass in patient treatment populations.

The term "osteogenically effective" as used herein, means that amount which effects the turnover of mature bone. As used herein, an osteogenically effective dose is also "pharmaceutically effective."

The term "treatment" or "treating" as used herein shall mean (1) providing a subject with an amount of anhydrous alendronate sodium sufficient to act prophylactically to prevent the development of a weakened and/or unhealthy state; and/or (2) providing a subject with a sufficient amount of anhydrous alendronate sodium so as to alleviate or eliminate a disease state and/or the symptoms of a disease state, and a weakened and/or unhealthy state.

Pharmaceutical formulations of the invention which include anhydrous alendronate sodium for administration will generally include an osteogenically effective amount of anhydrous alendronate sodium to promote bone growth, in addition to a pharmaceutically acceptable excipient.

The precise therapeutic dosage of anhydrous alendronate sodium will vary with the age, size, sex and condition of the subject, the nature and seventy of the disorder to be treated, and the like; thus, a precise effective amount cannot be specified in advance and will be determined by the caregiver. However, appropriate amounts may be determined by routine experimentation with animal models, as described below. In general terms, an effective dose for alendronate disodium is about 0.01 to 1 mg/kg per day of body weight. Particularly useful dosages are 2.72, 5.44, 10.88 and 43.52 mg per day/per person of anhydrous alendronate monosodium (equivalent to 2.5, 5.0, 10 and 40 mg free acid equivalents) per day per person.

The pharmaceutical composition described herein contains anhydrous alendronate monosodium salt in an amount of about 0.005 to 1.0 gram per gram of composition.

The pharmaceutical compositions according to the present invention containing anhydrous alendronate sodium may be prepared for use in the form of capsules or tablets for oral administration or for systemic use. The compositions are advantageously prepared together with inert carriers such as sugars (saccharose, glucose, lactose), starch and derivatives, cellulose and derivatives, gums, fatty acids and their salts, polyalcohols, talc, aromatic esters, and the like.

The composition can also be prepared by direct compression of a dry mix formulation as described in U.S. Pat. No. 5,358,941 (assigned to Merck & Co. Inc.). Particularly useful diluents in this composition are anhydrous lactose and microcrystalline cellulose.

Some typical pharmaceutical formulations (200 mg oral tablets) containing anhydrous alendronate sodium are shown below:

TABLETS (WHITE), 200 MG

	COMPOSITION IN MG/TABLET			
INGREDIENT	2.5 mg**	5.0 mg**	10.0 mg**	40.0 mg**
AAS*	2.72	5.44	10.88	43.52
Lactose Anhydrous NF	114.28	111.55	106.12	73.48
Microcrystalline Cellulose NF (Avicel PH 102)	80.0	80.0	80.0	80.0
Magnesium Stearate NF	1.00	1.00	1.00	1.00
Croscarmellose Sodium NF (Ac-Di-Sol)	2.00	2.00	2.00	2.00
Total	200	200	200	200

*AAS, anhydrous alendronate monosodium salt-active ingredient.
**Anhydrous alendronate free acid equivalent, 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid.
Note:
The amounts of inactive ingredients may vary ± 10%

The methods and compositions of the invention are useful for treating bone fractures, defects and disorders which result from the pathological conditions of osteoporosis, osteoarthritis, Paget's disease, osteohalisteresis, osteomalacia, bone loss resulting from multiple myeloma other forms of cancer, bone loss resulting from side effects of disuse, other medical treatment (such as steroids), rheumatoid-related and age-related loss of bone mass.

The composition of the instant invention is also useful in lessening the risk of vertebral and non-vertebral fractures in osteoporotic post-menopausal women.

The composition described herein is also useful for the prevention and treatment of periodontal disease (see U.S. Pat. No. 5,270,365); to prevent or treat loosening of orthopedic implant devices; and, to lessen the risk in osteoporotic women of vertebral fractures, which composition can be administered in a protocol over a three year period.

The composition can also be used in combination with prostaglandins (see WO 94/06750), estrogen (see WO 94/14455), or growth hormone secretagogues to treat osteoporosis and the above-described conditions associated with abnormalities in bone resorption.

The following Example is given to illustrate the carrying out of the invention as contemplated by the inventors and should not be construed as being a limitation on the scope and spirit of the invention.

EXAMPLE

Preparation of 4-Amino-1-Hydroxy-Butylidene-1,1-Bisphosphonic Acid Monosodium Salt Anhydrate

To a suspension of 4-amino-1-hydroxy-1,1-diphosphonic acid (4.02 g) in 150 ml of distilled water was added with stirring aqueous sodium hydroxide (0.5N) until the pH of the solution was 4.40. The stirred solution was triturated with 200 ml ethanol (absolute) to give a suspension of a fine white solid which was chilled at 5 degrees C. overnight. The obtained solid was collected by vacuum filtration, air dried, and then dried in vacuo at 100 degrees C. at 0.2 torr for 18 hours over P_2O_5 to yield 3.38 g, (91%) yield of the titled compound. A sample was submitted for CHN analysis;

For $C_4H_{12}NO_7P_2Na$:

Anal.: C, 17.72; H, 4.46; N, 5.16

Found: C, 17.56; H, 4.67; N, 5.15

Melting Point of the solid was 244–245 degrees C.(d.)

The obtained titled salt displays a unique X-ray diffraction pattern.

Solubility of the anhydrous monosodium salt in water is about 300 mg/ml as compared to the free acid which is 8 mg/ml. However, above 40 mg/ml, the trihydrate precipitates out of the aqueous solution.

The solution pH of the monosodium salt at 40 mg/ml. is 4.4, as compared to the free acid which is pH 2.2 at 8 mg/ml.

The water adsorption by the anhydrous salt at lower humidities is quite slow.

What is claimed is:

1. A method for treating bone resorption in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of anhydrous 4-amino-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt in a pharmaceutically acceptable carrier.

2. A method for preventing bone resorption in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of anhydrous 4-amino-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt in a pharmaceutically acceptable carrier.

3. A method for inhibiting bone resorption in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of anhydrous 4-amino-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt in a pharmaceutically acceptable carrier.

4. A method for promoting bone growth in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of anhydrous 4-amino-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt in a pharmaceutically acceptable carrier.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO: 6,008,207

DATED: 12/28/1999

INVENTOR(S): G.S. BRENNER et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE CLAIMS:

At Col. 4, Claim 1, line 41, delete the compound "4-amino-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt" and insert therefor -- 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt --.

At Col. 4, Claim 2, line 46, delete the compound "4-amino-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt" and insert therefor -- 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt --.

At Col. 4, Claim 3, line 51, delete the compound "4-amino-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt" and insert therefor -- 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt --.

At Col. 4, Claim 4, line 56, delete the compound "4-amino-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt" and insert therefor -- 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt --.

Signed and Sealed this

Thirty-first Day of October, 2000

Attest:

Q. TODD DICKINSON

Attesting Officer

Director of Patents and Trademarks

EXHIBIT 5

US006090410A

United States Patent [19]

Bechard et al.

[11] **Patent Number: 6,090,410**

[45] **Date of Patent: *Jul. 18, 2000**

[54] **DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS**

[75] Inventors: **Simon R. Bechard**, Quebec, Canada; **Kenneth A. Kramer**, Green Lane; **Ashok V. Katdare**, Norristown, both of Pa.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/141,782**

[22] Filed: **Aug. 28, 1998**

Related U.S. Application Data

[63] Continuation of application No. 08/946,849, Oct. 8, 1997, Pat. No. 5,882,656, which is a continuation of application No. 08/454,100, Jul. 26, 1995, which is a continuation of application No. PCT/US93/11172, Nov. 17, 1993, Pat. No. 5,681,590, which is a continuation of application No. 07/984,399, Dec. 2, 1992, Pat. No. 5,358,941.

[51] **Int. Cl.**[7] **A61K 9/20**; A61K 9/14

[52] **U.S. Cl.** **424/464**; 424/465; 424/494

[58] **Field of Search** 424/464, 465, 424/494

[56] **References Cited**

U.S. PATENT DOCUMENTS

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4,621,077	11/1986	Rosini et al.	514/108
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5,158,944	10/1992	Makino et al.	514/167
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5,681,590	10/1997	Bechard et al.	424/464

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Lachman et al., The Theory and Practice of Industrial Pharmacy, 3rd edition (1986), p. 326.

Remington's Pharmaceutical Science. 15th Edition, Mack Pub. Co., Easton, PA. pp. 1586–1588.

Primary Examiner—Carlos Azpuru

Attorney, Agent, or Firm—Anthony D. Sabatelli; Joanne M. Giesser

[57] **ABSTRACT**

Pharmaceutical compositions of bisphosphonic acids, and salts thereof, are prepared by direct compression/dry mix tablet formulation. These pharmaceutical compositions are useful in the treatment of disturbances involving calcium or phosphate metabolism, in particular, the treatment and prevention of diseases involving bone resorption, especially osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease.

13 Claims, No Drawings

DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS

CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation of application Ser. No. 08/946,849, filed Oct. 8, 1997 now U.S. Pat. No. 5,882,656, which in turn is a continuation of application Ser. No. 08/454,100, filed Jul. 26, 1995, now U.S. Pat. No. 5,681,590, issued Oct. 28, 1997, which in turn is a continuation PCT/US93/11172, filed Nov. 17, 1993, which is a continuation of U.S. patent application Ser. No. 07/984,399, filed Dec. 2, 1992, now U.S. Pat. No. 5,358,941, issued Oct. 25, 1994.

BACKGROUND OF THE INVENTION

The pharmaceutical industry employs various methods for compounding pharmaceutical agents in tablet formulations. In particular, wet granulation is one of the most prevalent methods.

A variety of bisphosphonic acids have been disclosed as being useful in the treatment and prevention of diseases involving bone resorption. Representative examples may be found in the following: U.S. Pat. No. 3,962,432; U.S. Pat. No. 4,054,598; U.S. Pat. No. 4,267,108; U.S. Pat. No. 4,327,039; U.S. Pat. No. 4,621,077; U.S. Pat. No. 4,624,947; U.S. Pat. No. 4,746,654; U.S. Pat. No. 4,922,077; and EPO Patent Pub. No. 0,252,504. Standard methods for tablet formulation of bisphosphonic acids, however, suffer serious difficulties.

In particular, bisphosphonic acids which bear a basic nitrogen-containing functionality may interact with the lactose of standard formulations resulting in discoloration, instability and potency loss. This degradation of the active ingredient is particularly pronounced in the presence of water and/or elevated temperature. It is speculated that this incompatibility is specifically due to the Maillard (or "browning") reaction in which the free amino group of the bisphosphonic acid reacts with the "glycosidic" hydroxyl group of a sugar (such as lactose) ultimately resulting in the formation of brown pigmented degradates. Although this problem may be avoided by the elimination of lactose, the use of lactose as an inert diluent is generally desirable.

The present invention solves this problem by providing a tablet formulation and process therefor that avoids such interaction between the bisphosphonic acid and the lactose in the formulation. In addition, the present invention also provides a processing advantage since it requires only blending of the ingredients without granulation or addition of water prior to compression.

DESCRIPTION OF THE INVENTION

The present invention is directed in a first embodiment to a process for the preparation of pharmaceutical compositions of bisphosphonic acids by direct compression (dry mix) tablet formulation. This process employs a blend of a bisphosphonic acid and minimal amounts of other processing aids with no water added. The tablet formulation is prepared by mixing the formulation ingredients with no hydration (i.e. no additional water is added to the mixture) prior to direct compression.

More specifically, this embodiment of the present invention concerns a process for the preparation of a tablet containing a bisphosphonic acid as an active ingredient which process comprises:

forming a mixture by mixing the active ingredient with:

a diluent,

a dry binder,

a disintegrant,

and optionally one or more additional ingredients selected from the group consiting of: compression aids, flavors, flavor enhancers, sweeteners and preservatives;

lubricating the mixture with a lubricant; and

compressing the resultant lubricated mixture into a desired tablet form.

The disclosed process may be used to prepare solid dosage forms, particularly tablets, for medicinal administration.

Preferred diluents include lactose. In particular, anydrous lactose is preferred from the flow processing point of view, although hydrous fast flow lactose may also be employed.

A preferred dry binder is cellulose. In articular, microcrystalline cellulose is preferred. Microcrystalline cellulose is available commercially under the trade name "Avicel" from FMC Corporation.

The disintegrant may be one of several modified starches or modified cellulose polymers, in particular, crosscarmellose sodium is preferred. Crosscarmellose sodium NF Type A is commercially available under the trade name "Ac-di-sol".

Preferred lubricants include magnesium stearate.

Examples of the bisphosphonic acids which may be employed as active ingredients in the instant invention include:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;

or a pharmaceutically acceptable salt thereof.

Methods for the preparation of bisphosphonic acids may be found in, e.g., U.S. Pat. No. 3,962,432; U.S. Pat. No. 4,054,598; U.S. Pat. No. 4,267,108; U.S. Pat. No. 4,327,039; U.S. Pat. No. 4,407,761; U.S. Pat. No. 4,621,077; U.S. Pat. No. 4,624,947; U.S. Pat. No. 4,746,654; U.S. Pat. No. 4,922,077; and EPO Patent Pub. No. 0,252,504. In particular, methods for the preparation of 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate may be found in U.S. Pat. No. 4,407,761 and U.S. Pat. No. 4,922,077, respectively.

The pharmaceutically acceptable salts of bisphosphonic acids may also be employed in the instant invention. Examples of base salts of bisphosphonic acids include ammonium salts, alkali metal salts such as potassium and sodium (including mono-, di- and tri-sodium) salts (which are preferred), alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. The non-toxic, physiologically acceptable salts are preferred.

The salts may be prepared by methods known in the art, such as in U.S. Pat. No. 4,922,077.

In the present invention it is preferred that the bisphosphonic acid is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid. It is even more preferred that the bisphosphonic acid is a sodium salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, in particular, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

Another embodiment of the present invention is a direct compression pharmaceutical composition, such as a tablet, comprising a bisphosphonic acid, which is prepared by the disclosed process. In general, these pharmaceutical compositions comprise by weight, about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; and from about 60 to 99.5% by weight of processing aids with no water added. More specifically, the processing aids are a diluent, a dry binder, a disintegrant and a lubricant. Preferred processing aids include: anhydrous lactose or hydrous fast flow lactose; microcrystalline cellulose; croscarmallose sodium; and magnesium stearate.

Preferred pharmaceutical compositions comprise about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; about 10 to 80% by weight of anhydrous lactose or hydrous fast flow lactose; about 5 to 50% by weight of microcrystalline cellulose; about 0.5 to 10% by weight of croscarmallose sodium; and about 0.1 to 5% by weight of magnesium stearate.

The preferred pharmaceutical compositions are generally in the form of tablets. The tablets may be, for example, from 50 mg to 1.0 g in net weight, more preferably 100 to 500 mg net weight, and even more preferably 200 to 300 mg net weight.

More preferred pharmaceutical compositions in accordance with the present invention comprise: about 0.5 to 25% by weight of a bisphosphonic acid selected from 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 30 to 70% by weight of anhydrous lactose or hydrous fast flow lactose; about 30 to 50% by weight of microcrystalline cellulose; about 0.5 to 5% by weight of croscarmallose sodium; and about 0.1 to 2% by weight of magnesium stearate.

Especially preferred pharmaceutical compositions comprise about 1 to 25% of the active ingredient, about 40 to 60% by weight of anhydrous lactose; about 35 to 45% by weight of microcrystalline cellulose; about 0.5 to 2% by weight of croscarmallose sodium; and about 0.1 to 1% by weight of magnesium stearate. Preferred pharmaceutical compositions as envisioned for commercial development are as follows.

Tablets of 2.5 mg potency free acid:

about 1.63. by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 56.87% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 17% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 5 mg potency free acid:

about 3.25% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 55.25% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 25 mg potency free acid:

about 16.4% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 42.1% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 50 mg potency free acid:

about 21.8% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 36.7% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

The pharmaceutical tablet compositions of the present invention may also contain one or more additional formulation ingredients may be selected from a wide variety of excipients known in the pharmaceutical formulation art. According to the desired properties of the tablet, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparing tablet compositions. Such ingredients include, but are not limited to, diluents, compression aids, disintegrants, lubricants, binders, flavors, flavor enhancers, sweetenter and preservatives.

The term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes, whether coated or uncoated. Substances which may be used for coating include hydroxypropylmethylcellulose, hydroxypropylcellulose, titanium oxide, talc, sweeteners, and colorants.

The pharmaceutical compositions of the present invention are useful in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. These diseases can be divided into two categories:

1. Abnormal (ectopic) depositions of calcium salts, mostly calcium phosphate, pathological hardening of tissues and bone malformations.
2. Conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in bone augmentation. A reduction in bone resorption can aleviate the pain associated with osteolytic lesions and reduce the incidence and/or growth of those lesions.

These diseases include: osteoporosis (including estrogen defficiency, immobilization, glucocorticoid induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcimia, metastatic bone disease, peridontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany.

Increased bone resorption can be accompanied by pathologically high calcium and phosphate concentrations in the plasma, which would be aleviated by use of the instant pharmaceutical compositons.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

EXAMPLE 1

Procedure for Manufacturing 5 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic Acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	6.55 mg	26.2 g
Anhydrous Lactose, NF	110.45 mg	441.8 g
Microcrystaline Cellulose NF	80.0 mg	320.0 g
Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0 g
Croscarmellose Sodium NF Type A	2.00 mg	8.0 g

The active ingredient (equivalent to 5 mg anhydrous free acid per tablet) was premixed with ⅓ of the microcrystaline cellulose NF and ½ of the anhydrous lactose NF in a ribbon blender for 5 minutes at 20 RPM. To the premix was added the remaining ⅔ of the microcrystaline cellulose NF and the remaining ½ of the anhydrous lactose NF. This was blended for 10 minutes at 20 RPM. Crosscarmellose sodium was added to the blended powders and mixed for 5 minutes at 20 RPM. Finally the magnesium stearate was added to the mixture by passing through a 90 mesh screen and blended for an additional 5 minutes at 20 RPM. The lubricated mixture was compressed to provide tablets of 5 mg active ingredient.

EXAMPLE 2

Procedure for Manufacturing 25 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic Acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	32.75 mg	131.0 g
Anhydrous Lactose, NF	84.25 mg	337.0 g
Microcrystaline Cellulose NF	80.0 mg	320.0 g
Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0 g
Croscarmellose Sodium NF Type A	2.00 mg	8.0 g

Tablets were prepared using essentially the procedure of Example 1.

EXAMPLE 3

Procedure for Manufacturing 50 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic Acid

Ingredients	Per Tablet	Per 2,500 Tablets
Active ingredient (monosodium sa1t trihydrate)	65.5 mg	163.75 g
Anhydrous Lactose, NF	110.0 mg	275.0 g
Microcrystaline Cellulose NF	120.0 mg	300.0 g
Magnesium Stearate Impalpable Powder NF	1.5 mg	3.75 g
Croscarmellose Sodium NF Type A	3.0 mg	7.5 g

Tablets were prepared using essentially the procedure of Example 1.

EXAMPLE 4

Stability Studies

Tablet formulations of the active ingredient (equivalent to 5 mg anhydrous free 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid per tablet) were prepared under different conditions with differing excipients. The tablets were subjected to stability studies under open dish conditions at 40° C./75% relative humidity. The following observations were noted:

1. Tablet discoloration occured within 2 weeks in formulations which were manufactured by wet granulation and contained anhydrous lactose.
2. Tablet discoloration occured within 4 weeks in formulations which were manufactured by wet granulation and contained hydrous lactose.
3. There was no tablet discoloration after 4 weeks in formulations which manufactured as a direct compression (dry mix) formulation. Assay of the active ingredient confirmed that there was no loss of potency or formation of degradates over the same time period.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

What is claimed is:

1. A pharmaceutical composition comprising from about 0.5 to 40% by weight of a bisphosphonic acid or a pharmaceutically acceptable salt thereof and from about 60% to 99.5% by weight of excipients, said excipients comprising a diluent selected from the group consisting of anhydrous lactose and hydrous fast flow lactose, a binder, a disintegrant, and a lubricant.

2. A pharmaceutical composition comprising from about 0.5 to 40% by weight of a nitrogen containing bisphosphonic acid or a pharmaceutically acceptable salt thereof and from about 60% to 99.5% by weight of excipients, said excipients comprising a diluent selected from the group consisting of anhydrous lactose and hydrous fast flow lactose, a binder, a disintegrant, and a lubricant.

3. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is 4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is 1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is 4-(hydroxymethylene-1,1-bisphosphonic acid) piperidine or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition according to claim 2 wherein said nitrogen containing bisphosphonic acid or pharmaceutically acceptable salt thereof is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

12. A pharmaceutical composition comprising by weight about 0.5 to 40% by weight of an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid; N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid; 4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid; 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid; 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid; 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid; 1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; 4-(hydroxymethylene-1,1-bisphosphonic acid) piperidine; or a pharmaceutically acceptable salt thereof; and from about 60% to 99.5% by weight of excipients comprising: a diluent selected from the group consisting of anhydrous lactose and hydrous fast flow lactose, a binder, a disintegrant, and a lubricant.

13. A composition according to any of claims 1–12 wherein said diluent is anhydrous lactose.

* * * * *

EXHIBIT 6

US006194004B1

(12) **United States Patent**
Bechard et al.

(10) **Patent No.: US 6,194,004 B1**
(45) **Date of Patent: *Feb. 27, 2001**

(54) **DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/432,859**

(22) Filed: **Nov. 2, 1999**

Related U.S. Application Data

(62) Continuation of application No. 09/141,782, filed on Aug. 28, 1998, now Pat. No. 6,090,410, which is a continuation of application No. 08/946,849, filed on Oct. 8, 1997, now Pat. No. 5,882,656, which is a continuation of application No. 08/454,100, filed as application No. PCT/US93/11172 on Nov. 17, 1993, now Pat. No. 5,681,590, which is a continuation of application No. 07/984,399, filed on Dec. 2, 1992, now Pat. No. 5,358,941.

(51) **Int. Cl.**[7] **A61K 9/20**; A01N 57/02

(52) **U.S. Cl.** **424/464**; 424/465; 514/102; 514/104

(58) **Field of Search** 424/464, 465; 514/102, 104

(56) **References Cited**

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4,267,108	5/1981	Blum et al.	260/326.61
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Primary Examiner—Carlos Azpuru
(74) *Attorney, Agent, or Firm*—Anthony D. Sabatelli; Joanne M. Giesser

(57) **ABSTRACT**

Pharmaceutical compositions of bisphosphonic acids, and salts thereof, are prepared by direct compression/dry mix tablet formulation. These pharmaceutical compositions are useful in the treatment of disturbances involving calcium or phosphate metabolism, in particular, the treatment and prevention of diseases involving bone resorption, especially osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease.

25 Claims, No Drawings

DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS

CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. Ser. No. 09/141,782, filed Aug. 28, 1998, now U.S. Pat. No. 6,090,410 which in turn is a continuation of U.S. Ser. No. 08/946,849, filed Oct. 8, 1997, now U.S. Pat. No. 5,882,656, issued Mar. 16, 1999, which in turn is a continuation of U.S. Ser. No. 08/454,100, filed Jul. 26, 1995, now U.S. Pat. No. 5,681,590, issued Oct. 28, 1997, which in turn is a U.S. National Phase Application of International Patent Application No. PCT/US93/11172, filed Nov. 17, 1993, which is a continuation of U.S. Ser. No 07/984,399, filed Dec. 2, 1992, now U.S. Pat. No. 5,358,941, issued Oct. 25, 1994.

BACKGROUND OF THE INVENTION

The pharmaceutical industry employs various methods for compounding pharmaceutical agents in tablet formulations. In particular, wet granulation is one of the most prevalent methods.

A variety of bisphosphonic acids have been disclosed as being useful in the treatment and prevention of diseases involving bone resorption. Representative examples may be found in the following: U.S. Pat. No. 3,962,432; U.S. Pat. No. 4,054,598; U.S. Pat. No. 4,267,108; U.S. Pat. No. 4,327,039; U.S. Pat. No. 4,621,077; U.S. Pat. No. 4,624,947; U.S. Pat. No. 4,746,654; U.S. Pat. No. 4,922,077; and EPO Patent Pub. No. 0,252,504. Standard methods for tablet formulation of bisphosphonic acids, however, suffer serious difficulties.

In particular, bisphosphonic acids which bear a basic nitrogen-containing functionality may interact with the lactose of standard formulations resulting in discoloration, instability and potency loss. This degradation of the active ingredient is particularly pronounced in the presence of water and/or elevated temperature. It is speculated that this incompatibility is specifically due to the Maillard (or "browning") reaction in which the free amino group of the bisphosphonic acid reacts with the "glycosidic" hydroxyl group of a sugar (such as lactose) ultimately resulting in the formation of brown pigmented degradates. Although this problem may be avoided by the elimination of lactose, the use of lactose as an inert diluent is generally desirable.

The present invention solves this problem by providing a tablet formulation and process therefor that avoids such interaction between the bisphosphonic acid and the lactose in the formulation. In addition, the present invention also provides a processing advantage since it requires only blending of the ingredients without granulation or addition of water prior to compression.

DESCRIPTION OF THE INVENTION

The present invention is directed in a first embodiment to a process for the preparation of pharmaceutical compositions of bisphosphonic acids by direct compression (dry mix) tablet formulation. This process employs a blend of a bisphosphonic acid and minimal amounts of other processing aids with no water added. The tablet formulation is prepared by mixing the formulation ingredients with no hydration (i.e. no additional water is added to the mixture) prior to direct compression.

More specifically, this embodiment of the present invention concerns a process for the preparation of a tablet containing a bisphosphonic acid as an active ingredient which process comprises:

forming a mixture by mixing the active ingredient with:
- a diluent,
- a dry binder,
- a disintegrant,
- and optionally one or more additional ingredients selected from the group consiting of: compression aids, flavors, flavor enhancers, sweeteners and preservatives;

lubricating the mixture with a lubricant; and

compressing the resultant lubricated mixture into a desired tablet form.

The disclosed process may be used to prepare solid dosage forms, particularly tablets, for medicinal administration.

Preferred diluents include lactose. In particular, anydrous lactose is preferred from the flow processing point of view, although hydrous fast flow lactose may also be employed.

A preferred dry binder is cellulose. In particular, microcrystalline cellulose is preferred. Microcrystalline cellulose is available commercially under the trade name "Avicel" from FMC Corporation.

The disintegrant may be one of several modified starches or modified cellulose polymers, in particular, crosscarmellose sodium is preferred. Crosscarmellose sodium NF Type A is commercially available under the trade name "Ac-di-sol".

Preferred lubricants include magnesium stearate.

Examples of the bisphosphonic acids which may be employed as active ingredients in the instant invention include:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propyl-idene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-(hydroxymethylene-1,1-bisphosphonic acid)-piperidine;

or a pharmaceutically acceptable salt thereof.

Methods for the preparation of bisphosphonic acids may be found in, e.g., U.S. Pat. No. 3,962,432; U.S. Pat. No. 4,054,598; U.S. Pat. No. 4,267,108; U.S. Pat. No. 4,327,039; U.S. Pat. No. 4,407,761; U.S. Pat. No. 4,621,077; U.S. Pat. No. 4,624,947; U.S. Pat. No. 4,746,654; U.S. Pat. No. 4,922,077; and EPQ Patent Pub. No. 0,252,504. In particular, methods for the preparation of 4-amino-1-hydroxy-butylidene-1, 1-bisphosphonic acid and 4-amino-1-hydroxy-butylidene-1, 1-bisphosphonic acid monosodium salt trihydrate may be found in U.S. Pat. No. 4,407,761 and U.S. Pat. No. 4,922,077, respectively.

The pharmaceutically acceptable salts of bisphosphonic acids may also be employed in the instant invention. Examples of base salts of bisphosphonic acids include ammonium salts, alkali metal salts such as potassium and sodium (including mono-, di- and tri-sodium) salts (which are preferred), alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. The

non-toxic, physiologically acceptable salts are preferred. The salts may be prepared by methods known in the art, such as in U.S. Pat. No. 4,922,077.

In the present invention it is preferred that the bisphosphonic acid is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid. It is even more preferred that the bisphosphonic acid is a sodium salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, in particular, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

Another embodiment of the present invention is a direct compression pharmaceutical composition, such as a tablet, comprising a bisphosphonic acid, which is prepared by the disclosed process. In general, these pharmaceutical compositions comprise by weight, about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; and from about 60 to 99.5% by weight of processing aids with no water added. More specifically, the processing aids are a diluent, a dry binder, a disintegrant and a lubricant. Preferred processing aids include: anhydrous lactose or hydrous fast flow lactose; microcrystalline cellulose; croscarmallose sodium; and magnesium stearate.

Preferred pharmaceutical compositions comprise about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; about 10 to 80% by weight of anhydrous lactose or hydrous fast flow lactose; about 5 to 50% by weight of microcrystalline cellulose; about 0.5 to 10% by weight of croscarmallose sodium; and about 0.1 to 5% by weight of magnesium stearate.

The preferred pharmaceutical compositions are generally in the form of tablets. The tablets may be, for example, from 50 mg to 1.0 g in net weight, more preferably 100 to 500 mg net weight, and even more preferably 200 to 300 mg net weight.

More preferred pharmaceutical compositions in accordance with the present invention comprise: about 0.5 to 25% by weight of a bisphosphonic acid selected from 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 30 to 70% by weight of anhydrous lactose or hydrous fast flow lactose; about 30 to 50% by weight of microcrystalline cellulose; about 0.5 to 5% by weight of croscarmallose sodium; and about 0.1 to 2% by weight of magnesium stearate.

Especially preferred pharmaceutical compositions comprise about 1 to 25% of the active ingredient, about 40 to 60% by weight of anhydrous lactose; about 35 to 45% by weight of microcrystalline cellulose; about 0.5 to 2% by weight of croscarmallose sodium; and about 0.1 to 1% by weight of magnesium stearate. Preferred pharmaceutical compositions as envisioned for commercial development are as follows.

Tablets of 2.5 mg potency free acid:

about 1.63% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 56.87% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 5 mg potency free acid:

about 3.25% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 55.25% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 25 mg potency free acid:

about 16.4% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 42.1% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 50 mg potency free acid:

about 21.8% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 36.7% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

The pharmaceutical tablet compositions of the present invention may also contain one or more additional formulation ingredients may be selected from a wide variety of excipients known in the pharmaceutical formulation art. According to the desired properties of the tablet, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparing tablet compositions. Such ingredients include, but are not limited to, diluents, compression aids, disintegrants, lubricants, binders, flavors, flavor enhancers, sweetenter and preservatives.

The term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes, whether coated or uncoated. Substances which may be used for coating include hydroxypropylmethylcellulose, hydroxypropyl-cellulose, titanium oxide, talc, sweeteners, and colorants.

The pharmaceutical compositions of the present invention are useful in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. These diseases can be divided into two categories:

1. Abnormal (ectopic) depositions of calcium salts, mostly calcium phosphate, pathological hardening of tissues and bone malformations.

2. Conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in bone augmentation. A reduction in bone resorption can aleviate the pain associated with osteolytic lesions and reduce the incidence and/or growth of those lesions.

These diseases include: osteoporosis (including estrogen defficiency, immobilization, glucocorticoid induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcimia, metastatic bone disease, peridontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany.

Increased bone resorption can be accompanied by pathologically high calcium and phosphate concentrations in the plasma, which would be aleviated by use of the instant pharmaceutical compositons.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

EXAMPLE 1

Procedure for Manufacturing 5 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	6.55 mg	26.2g
Anhydrous Lactose, NF	110.45 mg	441.8g
Microcrystaline Cellulose NF	80.0 mg	320.0g
Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0g
Croscarmellose Sodium NF Type A	2.00 mg	8.0g

The active ingredient (equivalent to 5 mg anhydrous free acid per tablet) was premixed with ⅓ of the microcrystaline cellulose NF and ½ of the anhydrous lactose NF in a ribbon blender for 5 minutes at 20 RPM. To the premix was added the remaining ⅔ of the microcrystaline cellulose NF and the remaining ½ of the anhydrous lactose NF. This was blended for 10 minutes at 20 RPM. Crosscarmellose sodium was added to the blended powders and mixed for 5 minutes at 20 RPM. Finally the magnesium stearate was added to the mixture by passing through a 90 mesh screen and blended for an additional 5 minutes at 20 RPM. The lubricated mixture was compressed to provide tablets of 5 mg active ingredient.

EXAMPLE 2

Procedure for Manufacturing 25 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 4,000 Tablets
Active ingredient (monosodium salt trihydrate)	32.75 mg	131.0g
Anhydrous Lactose, NF	84.25 mg	337.0g
Microcrystaline Cellulose NF	80.0 mg	320.0g
Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0g
Croscarmellose Sodium NF Type A	2.00 mg	8.0g

Tablets were prepared using essentially the procedure of Example 1.

EXAMPLE 3

Procedure for Manufacturing 50 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 2,500 Tablets
Active ingredient (monosodium salt trihydrate)	65.5mg	163.75 g
Anhydrous Lactose, NF	110.0mg	275.0 g

-continued

Procedure for Manufacturing 50 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

Ingredients	Per Tablet	Per 2,500 Tablets
Microcrystaline Cellulose NF	120.0mg	300.0 g
Nagnesium Stearate Impalpable Powder NF	1.5mg	3.75 g
Croscarmellose Sodium NF Type A	3.0mg	7.5 g

Tablets were prepared using essentially the procedure of Example 1.

EXAMPLE 4

Stability Studies

Tablet formulations of the active ingredient (equivalent to 5 mg anhydrous free 4-amino-1-hydroxy-butylidene-1, 1-bisphosphonic acid per tablet) were prepared under different conditions with differing excipients. The tablets were subjected to stability studies under open dish conditions at 40° C./75% relative humidity. The following observations were noted:

1. Tablet discoloration occured within 2 weeks in formulations which were manufactured by wet granulation and contained anhydrous lactose.

2. Tablet discoloration occured within 4 weeks in formulations which were manufactured by wet granulation and contained hydrous lactose.

3. There was no tablet discoloration after 4 weeks in formulations which manufactured as a direct compression (dry mix) formulation. Assay of the active ingredient confirmed that there was no loss of potency or formation of degradates over the same time period.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

What is claimed is:

1. A pharmaceutical composition comprising from about 0.5 to 40% by weight of a bisphosphonic acid or a pharmaceutically acceptable salt thereof and from about 60% to 99.5% by weight of excipients, said excipients comprising a diluent selected from the group consisting of anhydrous lactose and hydrous fast flow lactose, a binder, a disintegrant, and a lubricant, wherein said composition is coated.

2. A pharmaceutical composition according to claim **1** wherein said composition is coated with a substance selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcelluose, titanium oxide, talc, sweeteners, and colorants.

3. A pharmaceutical composition comprising from about 0.5 to 40% by weight of a nitrogen containing bisphosphonic acid or a pharmaceutically acceptable salt thereof and from about 60% to 99.5% by weight of excipients, said excipients comprising a diluent selected from the group consisting of anhydrous lactose and hydrous fast flow lactose, a binder, a disintegrant, and a lubricant, wherein said composition is coated.

4. A pharmaceutical composition according to claim 3 wherein said composition is coated with a substance selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcelluose, titanium oxide, talc, sweeteners, and colorants.

5. A pharmaceutical composition comprising from about 0.5 to 40% by weight of an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid; N-methyl-4-amino-1-hydroxybuytlidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1,-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid;

4-(hydroxymethylene-1,1-bisphosphonic acid) piperidine;

or a pharmaceutically acceptable salt thereof;

and from about 60% to 99.5% by weight of excipients, said excipients comprising a diluent selected from the group consisting of anhydrous lactose and hydrous fast flow lactose, a binder, a disintegrant, and a lubricant, wherein said composition is coated.

6. A pharmaceutical composition according to claim 5 wherein said composition is coated with a substance selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcelluose, titanium oxide, talc, sweeteners, and colorants.

7. A pharmaceutical composition according to claim 5 wherein said active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition according to claim 6 wherein said active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition according to claim 5 wherein said active ingredient is N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition according to claim 6 wherein said active ingredient is N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition according to claim 5 wherein said active ingredient is 4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition according to claim 6 wherein said active ingredient is 4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition according to claim 5 wherein said active ingredient is 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition according to claim 6 wherein said active ingredient is 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition according to claim 5 wherein said active ingredient is 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition according to claim 6 wherein said active ingredient is 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition according to claim 5 wherein said active ingredient is 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition according to claim 6 wherein said active ingredient is 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition according to claim 5 wherein said active ingredient is 1-hydroxy-2-[3-pyridyl] ethylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition according to claim 6 wherein said active ingredient is 1-hydroxy-2-[3-pyridyl] ethylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition according to claim 5 wherein said active ingredient is 4-(hydroxymethylene-1,1-bisphosphonic acid) piperidine or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition according to claim 6 wherein said active ingredient is 4-(hydroxymethylene-1,1-bisphosphonic acid) piperidine or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition according to any of claims 1–22 wherein said diluent is anhydrous lactose.

24. A pharmaceutical composition according to any of claims 1–22 wherein said composition is a tablet.

25. A pharmaceutical composition according to claim 23 wherein said composition is a tablet.

* * * * *

EXHIBIT 7

US005994329A

United States Patent [19]

Daifotis et al.

[11] **Patent Number: 5,994,329**

[45] **Date of Patent: Nov. 30, 1999**

[54] **METHOD FOR INHIBITING BONE RESORPTION**

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[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **09/134,214**

[22] Filed: **Aug. 14, 1998**

Related U.S. Application Data

[63] Continuation of application No. PCT/US98/14796, Jul. 17, 1998.

[60] Provisional application No. 60/053,535, Jul. 23, 1997, and provisional application No. 60/053,351, Jul. 22, 1997.

[51] **Int. Cl.**[6] **A61K 31/66**

[52] **U.S. Cl.** **514/108**

[58] **Field of Search** 514/108

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Attorney, Agent, or Firm—Anthony D. Sabatelli; Melvin Winokur

[57] **ABSTRACT**

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein.

44 Claims, 8 Drawing Sheets

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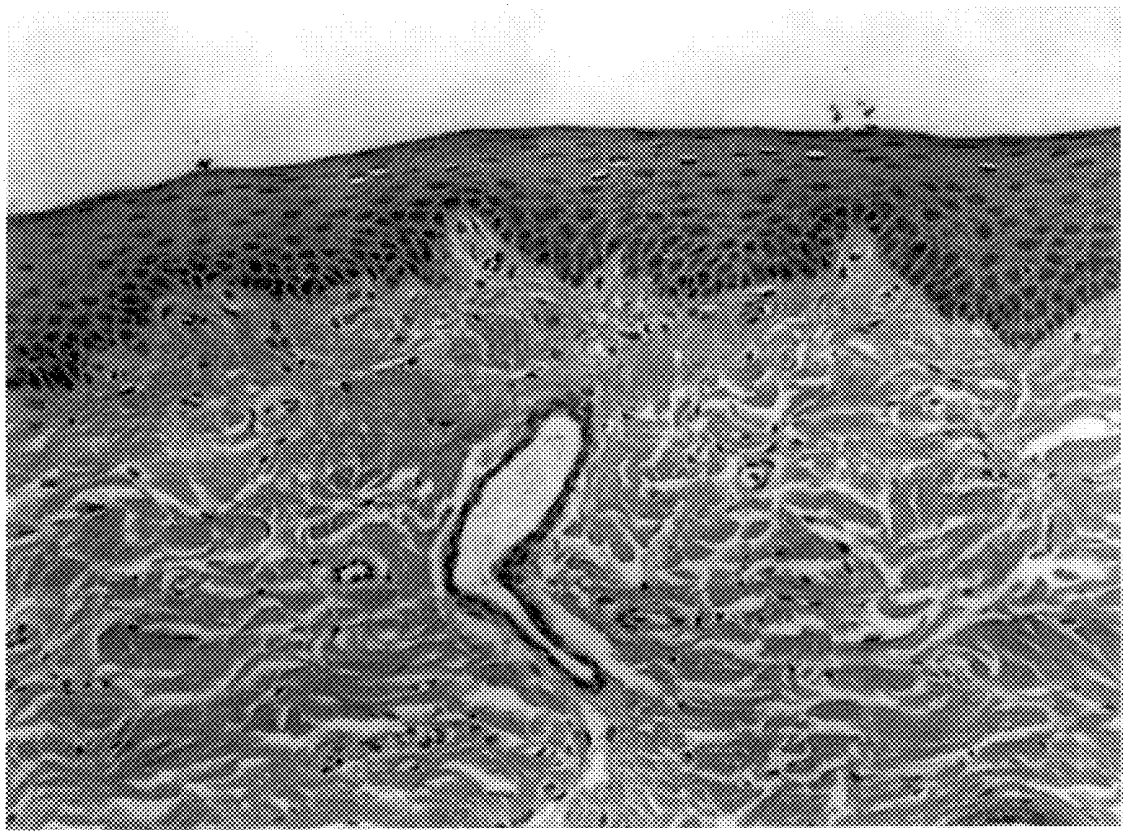


FIG. 1

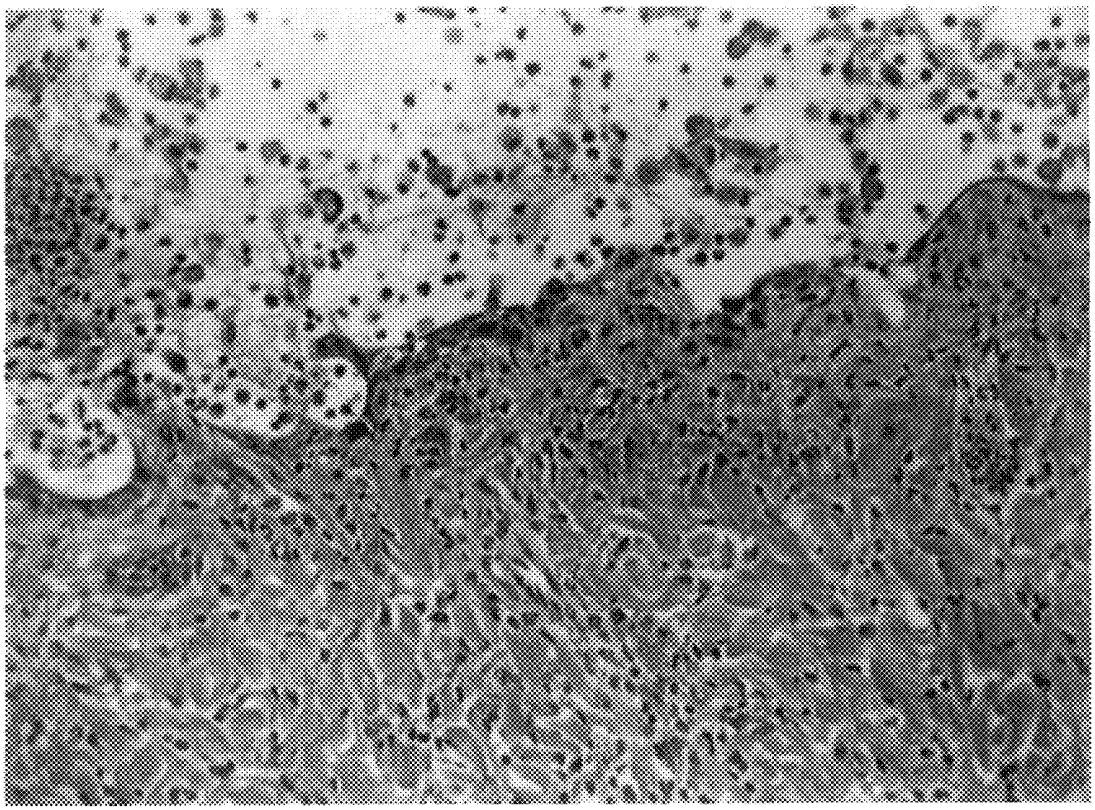


FIG.2

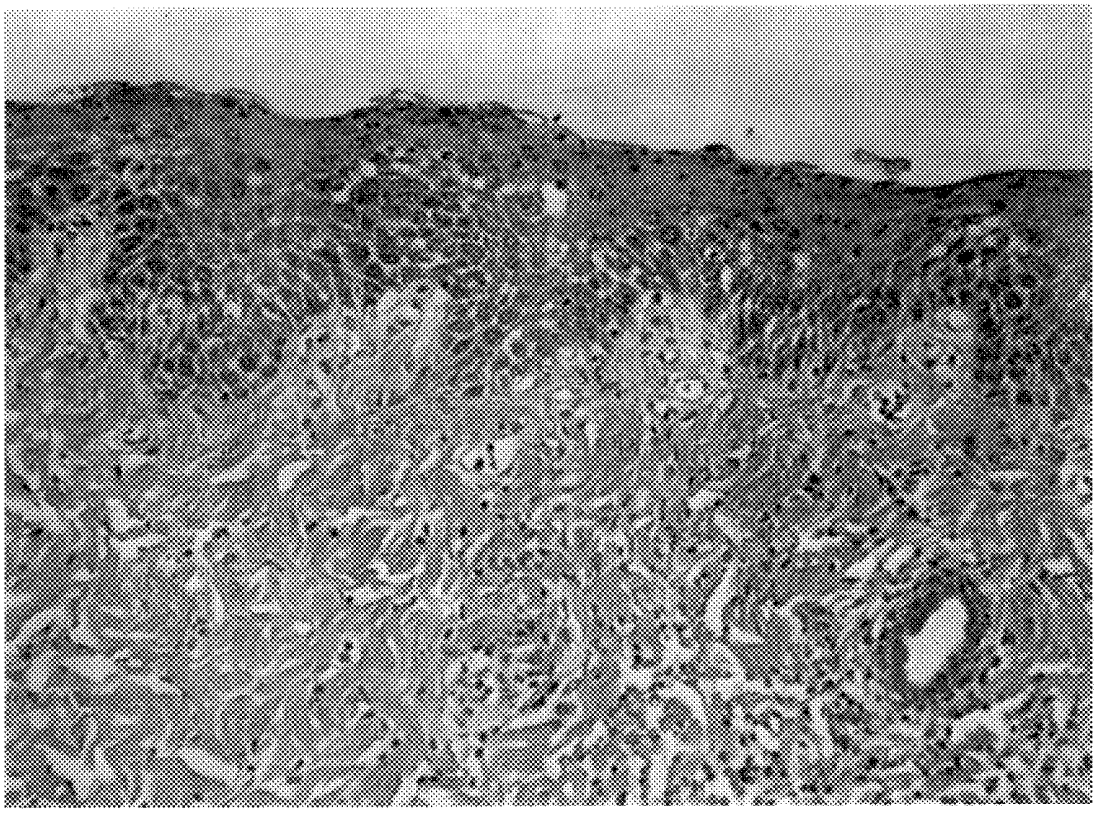


FIG.3

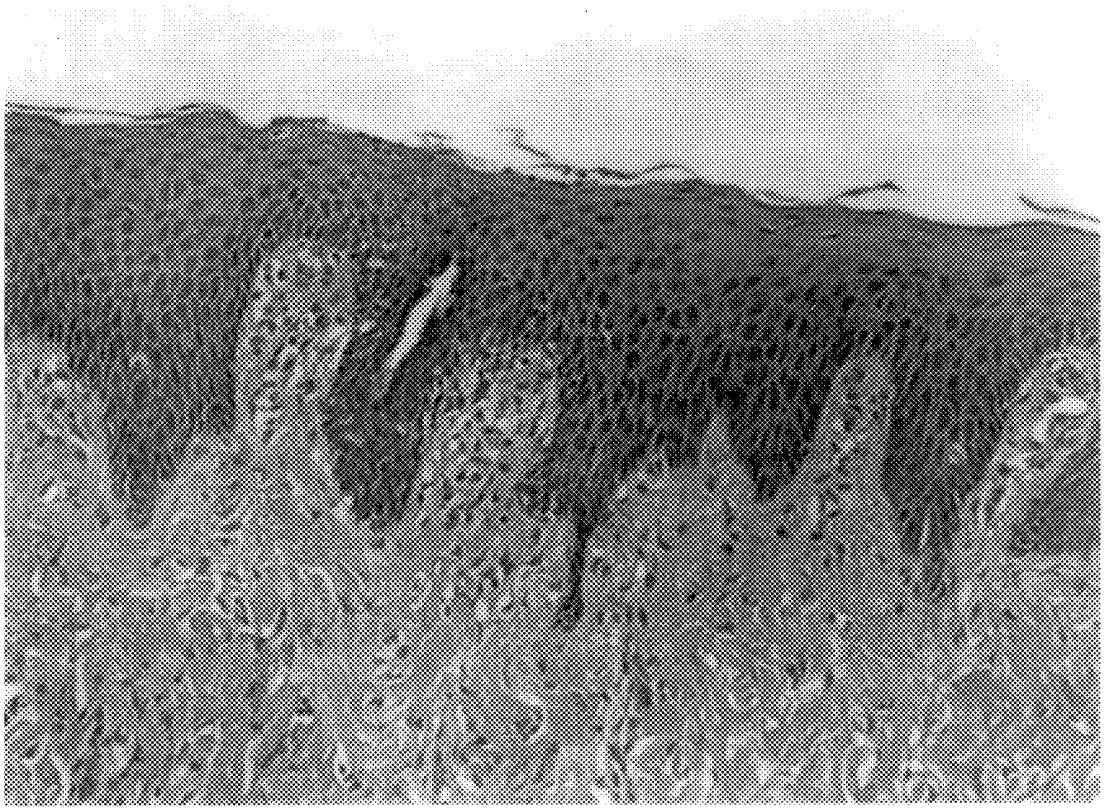


FIG.4

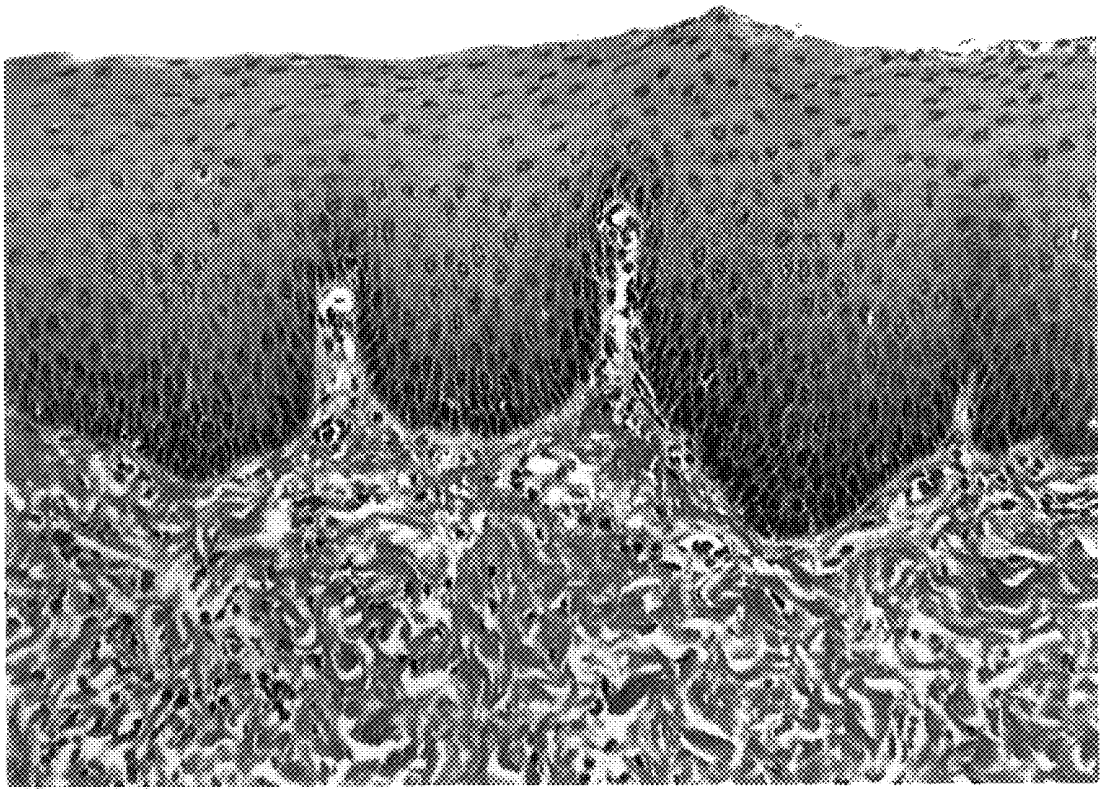


FIG. 5

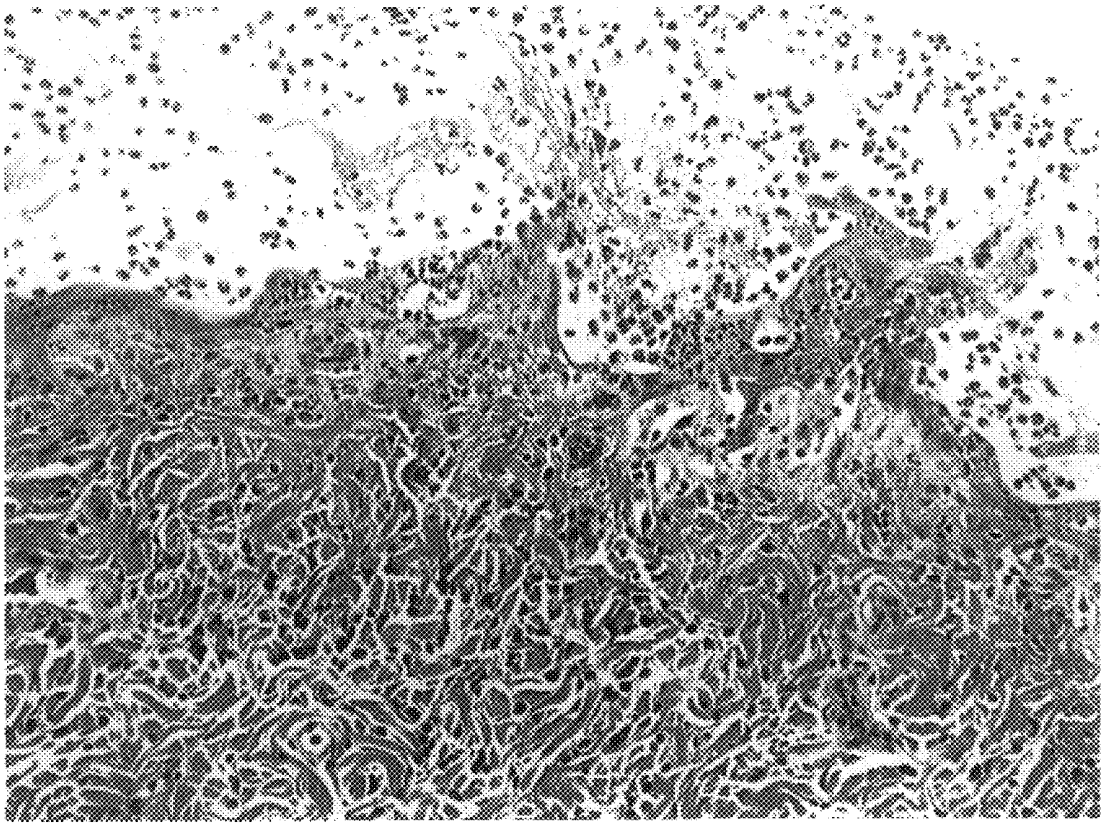


FIG.6

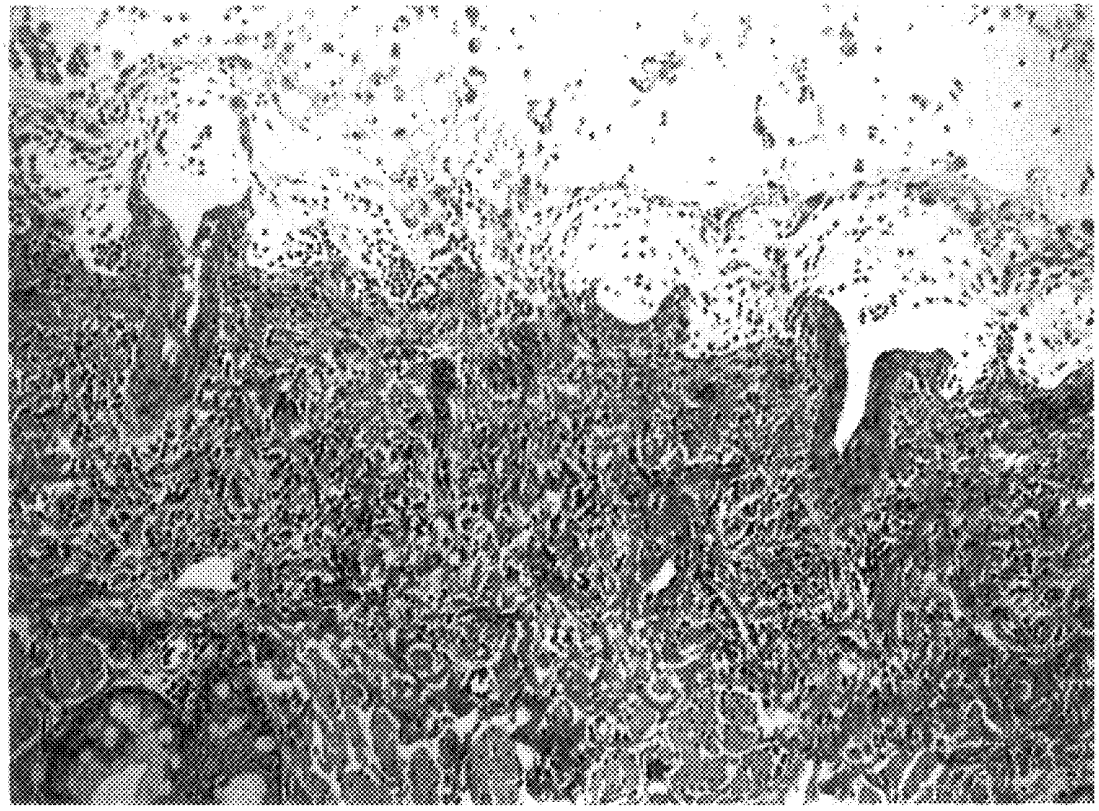


FIG. 7

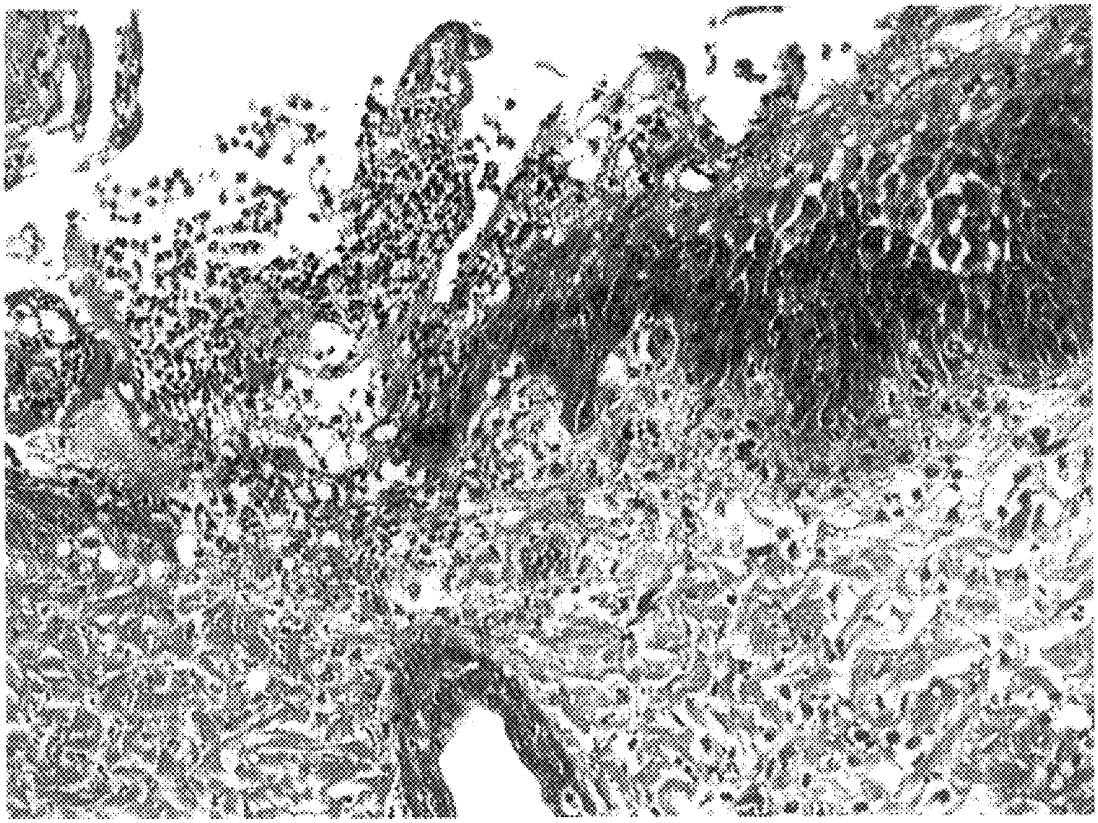


FIG.8

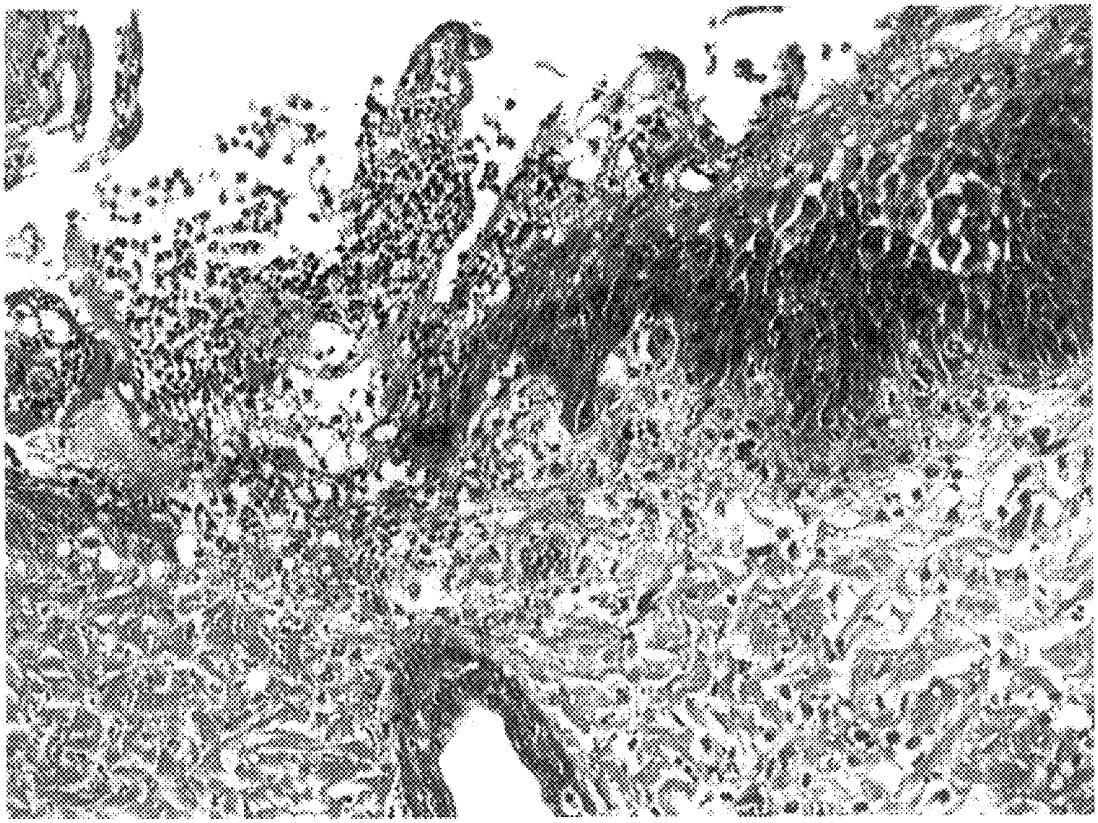


FIG.8

METHOD FOR INHIBITING BONE RESORPTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of PCT/US98/14796, filed Jul. 17, 1998, and also claims priority to U.S. provisional applications Serial Nos. 60/053,535, filed Jul. 23, 1997, and 60/053,351, filed Jul. 22, 1997, both now abandoned, the contents of all of the foregoing of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to oral methods for inhibiting bone resorption in a mammal while minimizing the occurrence of or potential for adverse gastrointestinal effects. These methods comprise orally administering to a mammal in need thereof of a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. The present invention also relates to pharmaceutical compositions and kits useful for carrying out these methods.

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, and hypercalcemia of malignancy. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone disorders caused by or associated with abnormal bone resorption. See H. Fleisch, *Bisphosphonates In Bone Disease, From The Laboratory To The Patient,* 2nd Edition, Parthenon Publishing (1995), which is incorporated by reference herein in its entirety.

At present, a great amount of preclinical and clinical data exists for the potent bisphosphonate compound alendronate. Evidence suggests that other bisphosphonates such as risedronate, tiludronate, ibandronate and zolendronate, have many properties in common with alendronate, including high potency as inhibitors of osteoclastic bone resorption. An older bisphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent bisphosphonates, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization. See Boyce, B. F., Fogelman, I., Ralston, S. et al. (1984) Lancet 1(8381), pp. 821–824 (1984), and Gibbs, C. J., Aaron, J. E.; Peacock, M. (1986) Br. Med. J. 292, pp. 1227–1229 (1986), both of which are incorporated by reference herein in their entirety.

Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. See B. J. Gertz et al., *Clinical Pharmacology of Alendronate Sodium, Osteoporosis Int.,* Suppl. 3:S13–16 (1993) and B. J. Gertz et al., *Studies of the oral bioavailability of alendronate, Clinical Pharmacology & Therapeutics,* vol. 58, number 3, pp. 288–298 (September 1995), which are incorporated by reference herein in their entirety. Intravenous administration has been used to overcome this bioavailability problem. However, intravenous administration is costly and inconvenient, especially when the patient must be given an intravenous infusion lasting several hours on repeated occasions.

If oral administration of the bisphosphonate is desired, relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. To offset this low bioavailability, it is generally recommended that the patient take the bisphosphonate on an empty stomach and fast for at least 30 minutes afterwards. However, many patients find the need for such fasting on a daily basis to be inconvenient. Moreover, oral administration has been associated with adverse gastrointestinal effects, especially those relating to the esophagus. See Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate has been associated with esophageal ulcers. See E. G. Lufkin et al., *Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International,* 4: 320–322 (1994), which is incorporated by reference herein in its entirety. Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. See P. C. De Groen, et al., *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1016–1021 (1996), D. O. Castell, *Pill Esophagitis—The Case of Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1058–1059 (1996), and U. A. Liberman et al., *Esophagitis and Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1069–1070 (1996), which are incorporated by reference herein in their entirety. The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. See C. H. Chestnut et al., *Alendronate Treatment of the Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine,* vol. 99, pp. 144–152, (August 1995), which is incorporated by reference herein in its entirety. Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fall into two categories: (1) those therapies utilizing continuous daily treatment, and (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

The continuous daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily dosing has the potential disadvantage of causing adverse gastrointestinal effects due to the repetitive, continuous, and additive irritation to the gastrointestinal tract. Also, because

bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

Cyclic treatment regimens were developed because some bisphosphonates, such as etidronate, when given daily for more than several days, have the disadvantage of actually causing a decline in bone mineralization, i.e. osteomalacia. U.S. Pat. No. 4,761,406, to Flora et al, issued Aug. 2, 1988, which is incorporated by reference herein in its entirety, describes a cyclic regimen developed in an attempt to minimize the decline in bone mineralization while still providing a therapeutic anti-resorptive effect. Generally, cyclic regimens are characterized as being intermittent, as opposed to continuous treatment regimens, and have both treatment periods during which the bisphosphonate is administered and nontreatment periods to permit the systemic level of the bisphosphonate to return to baseline. However, the cyclic regimens, relative to continuous dosing, appear to result in a decreased therapeutic antiresorptive efficacy. Data on risedronate suggests that cyclic dosing is actually less effective than continuous daily dosing for maximizing antiresorptive bone effects. See L. Mortensen, et al., *Prevention Of Early Postmenopausal Bone Loss By Risedronate, Journal of Bone and Mineral Research,* vol. 10, supp. 1, p. s140 (1995), which is incorporated by reference herein in its entirety. Furthermore, these cyclic regimens do not eliminate or minimize adverse gastrointestinal effects, because such regimens typically utilize periods of multiple daily dosing. Also, the cyclic regimens are cumbersome to administer and have the disadvantage of low patient compliance, and consequently compromised therapeutic efficacy. U.S. Pat. No. 5,366,965, to Strein, issued Nov. 22, 1994, which is incorpoated by reference herein in its entirety, attempts to address the problem of adverse gastrointestinal effects by administering a polyphosphonate compound, either orally, subcutaneously, or intravenously, according to an intermittent dosing schedule having both a bone resorption inhibition period and a no-treatment rest period. However, the regimen has the disadvantage of not being continuous and regular, and requires nontreatment periods ranging from 20 to 120 days. PCT Application No. WO 95/30421, to Goodship et al, published Nov. 16, 1995, which is incorporated by reference herein in its entirety, discloses methods for preventing prosthetic loosening and migration using various bisphosphonate compounds. Administration of a once weekly partial dose of the bisphosphonate is disclosed. However, the reference specifically fails to address the issue of adverse gastrointestinal effects or to disclose administration of larger or multiple dosages.

It is seen from current teachings that both daily and cyclic treatment regimens have shortcomings, and that there is a need for development of a dosing regimen to overcome these shortcomings.

In the present invention, it is found that the adverse gastrointestinal effects that can be associated with daily or cyclic dosing regimens can be minimized by administering the bisphosphonate at a relatively high unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other words, it is found that the administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency. This result is surprising in view of the teachings suggesting that adverse gastrointestinal effects would be expected to increase as a function of increasing bisphosphonate dosage. Such administration methods of the present invention would be especially beneficial in treating patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heatburn), ulcers, and other related disorders. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing. Also, patients would not need to keep track of a complex dosing regimen. The methods of the present invention are likely to have the advantage of promoting better patient compliance, which in turn can translate into better therapeutic efficacy.

It is an object of the present invention to provide methods for inhibiting bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods for treating abnormal bone resorption and the conditions associated therewith

It is another object of the present invention to provide methods for preventing abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods which are oral methods.

It is another object of the present invention to provide such methods in humans.

It is another object of the present invention to provide such methods in patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heatburn), ulcers, and other related disorders.

It is another object of the present invention to provide such methods while minimizing the occurrence of or potential for adverse gastronintestinal effects.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing interval selected from the group consisting of weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

It is another object of the present invention to provide such methods wherein the continuous dosing schedule is maintained until the desired therapeutic effect is achieved.

It is another object of the present invention to treat or prevent abnormal bone resorption in an osteoporotic mammal, preferably an osteoporotic human.

It is another object of the present invention to provide pharmaceutical compositions and kits useful in the methods herein.

These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to methods for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosages according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing, wherein said continuous schedule is maintained until the desired therapeutic effect is achieved for said mammal.

In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

In other embodiments, the present invention relates to methods for treating abnormal bone resorption in a mammal in need of such treatment.

In other embodiments, the present invention relates to methods for preventing abnormal bone resorption in a mammal in need of such prevention.

In other embodiments, the present invention relates to such methods useful in humans.

In other embodiments, the present invention relates to such methods useful in humans indentified as having or being susceptible to upper gastrointestinal disorders.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a mammal.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a human.

In other embodiments, the present invention relates to methods for inhibiting bone resorption, or treating or preventing abnormal bone resorption in a human comprising administering to said human from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

In other embodiments the present invention relates to a pharmaceutical composition comprising from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

All percentages and ratios used herein, unless otherwise indicated, are by weight. The invention hereof can comprise, consist of, or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of simulated gastric juice administered on five consecutive days.

FIG. **2** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL alendronate in simulated gastric juice administered on five consecutive days.

FIG. **3** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. **4** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. **5** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion of the last of 4 separate dosages of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice administered once per week, i.e. once every 7 days.

FIG. **6** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 4 days after infusion of the last of 8 separate dosages of 50 mL of 0.40 mg/mL alendronate in simulated gastric juice administered twice per week, i.e. once every 3–4 days.

FIG. **7** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL risedronate in simulated gastric juice administered on five consecutive days.

FIG. **8** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 4.0 mg/mL tiludronate in simulated gastric juice administered on five consecutive days.

DESCRIPTION OF THE INVENTION

The present invention relates to a method, preferably an oral method, for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects. The present invention relates to methods of treating or preventing abnormal bone resorption in a mammal in need of such treatment or prevention. The methods of the present invention comprise orally administering to a mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage, wherein said dosage is administered according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days. Typically, the continuous dosing schedule is maintained until the desired therapeutic effect is achieved for the mammal.

The present invention utilizes higher unit dosages of the bisphosphonate at each dosing point than has heretofore been typically administered, yet because of the dosing schedule chosen, the potential for adverse gastrointestinal effects are minimized. Moreover, the method is more convenient because the disadvantages associated with daily dosing are minimized.

The methods of the present invention are generally administered to mammals in need of bisphosphonate therapy. Preferably the mammals are human patients, particularly human patients in need of inhibiting bone

resorption, such as patients in need of treating or preventing abnormal bone resorption.

The administration methods of the present invention are especially useful in administering bisphosphonate therapy to human patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. GERD, esophagitis, dyspepsia, ulcers, etc. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

The term "pharmaceutically effective amount", as used herein, means that amount of the bisphosphonate compound, that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the bisphosphonate is a bone resorption inhibiting amount.

The term "minimize the occurrence of or potential for adverse gastrointestinal effects", as used herein, means reducing, preventing, decreasing, or lessening the occurrence of or the potential for incurring unwanted side effects in the gastrointestinal tract, i.e. the esophagus, stomach, intestines, and rectum, particularly the upper gastrointestinal tract, i.e. the esophagus and stomach. Nonlimiting adverse gastrointestinal effects include, but are not limited to GERD, esophagitis, dyspepsia, ulcers, esophageal irritation, esophageal perforation, abdominal pain, and constipation.

The term "abnormal bone resorption", as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. Alternatively, "abnormal bone resorption" can be associated with the formation of bone having an abnormal structure.

The term "bone resorption inhibiting", as used herein, means treating or preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to treatment or prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

The terms "continuous schedule" or "continuous dosing schedule", as used herein, mean that the dosing regimen is repeated until the desired therapeutic effect is achieved. The continuous schedule or continuous dosing schedule is distinguished from cyclical or intermittent administration.

The term "until the desired therapeutic effect is achieved", as used herein, means that the bisphosphonate compound is continuously administered, according to the dosing schedule chosen, up to the time that the clinical or medical effect sought for the disease or condition is observed by the clinician or researcher. For methods of treatment of the present invention, the bisphosphonate compound is continuously administered until the desired change in bone mass or structure is observed. In such instances, achieving an increase in bone mass or a replacement of abnormal bone structure with more normal bone structure are the desired objectives. For methods of prevention of the present invention, the bisphosphonate compound is continuously administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of bone mass density is often the objective. Nonlimiting examples of administration periods can range from about 2 weeks to the remaining lifespan of the mammal. For humans, administration periods can range from about 2 weeks to the remaining lifespan of the human, preferably from about 2 weeks to about 20 years, more preferably from about 1 month to about 20 years, more preferably from about 6 months to about 10 years, and most preferably from about 1 year to about 10 years.

Methods of the Present Invention

The present invention comprises methods for inhibiting bone resorption in mammals. The present invention also comprises treating abnormal bone resorption in mammals. The present invention also comprises methods for preventing abnormal bone resorption in mammals. In preferred embodiments of the present invention, the mammal is a human.

The methods of the present invention do not have the disadvantages of current methods of treatment which can cause or increase the potential for adverse gastrointestinal effects or which require cumbersome, irregular, or complicated dosing regimens.

The present invention comprises a continuous dosing schedule whereby a unit dosage of the bisphosphonate is regularly administered according to a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

By once-weekly dosing is meant that a unit dosage of the bisphosphonate is administered once a week, i.e. one time during a seven day period, preferably on the same day of each week. In the once-weekly dosing regimen, the unit dosage is generally administered about every seven days. A nonlimiting example of a once-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the once-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days falling within two different weekly periods.

By twice-weekly dosing is meant that a unit dosage of the bisphosphonate is administered twice a week, i.e. two times during a seven day period, preferably on the same two days of each weekly period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every three to four days. A nonlimiting example of a twice-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday and Wednesday. It is preferred that the unit dosages are not administered on the same or consecutive days, but the twice-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days within a weekly period or different weekly periods.

By biweekly dosing is meant that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every fourteen days. A nonlimiting example of a biweekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit

dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period, or different monthly periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens have a different periodicity and result in the administration of different numbers of dosages over long periods of time. For example, over a one year period, a total of about twenty four dosages would be administered according to the twice-monthly regimen (because there are twelve calendar months in a year), whereas a total of about twenty six dosages would be administered according to the biweekly dosing regimen (because there are about fifty-two weeks in a year).

In further embodiments or descriptions of the present invention, the unit dosage is given with a periodicity ranging from about once every 3 days to about once every 16 days.

The methods and compositions of the present invention are useful for inhibiting bone resorption and for treating and preventing abnormal bone resorption and conditions associated therewith. Such conditions include both generalized and localized bone loss. Also, the creation of bone having an abnormal structure, as in Paget's disease, can be associated with abnormal bone resorption. The term "generalized bone loss" means bone loss at multiple skeletal sites or throughout the skeletal system. The term "localized bone loss" means bone loss at one or more specific, defined skeletal sites.

Generalized boss loss is often associated with osteoporosis. Osteoporosis is most common in post-menopausal women, wherein estrogen production has been greatly diminished. However, osteoporosis can also be steroid-induced and has been observed in males due to age. Osteoporosis can be induced by disease, e.g. rheumatoid arthritis, it can be induced by secondary causes, e.g., glucocorticoid therapy, or it can come about with no identifiable cause, i.e. idiopathic osteoporosis. In the present invention, preferred methods include the treatment or prevention of abnormal bone resorption in osteoporotic humans.

Localized bone loss has been associated with periodontal disease, with bone fractures, and with periprosthetic osteolysis (in other words where bone resorption has occured in proximity to a prosthetic implant).

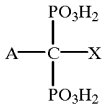
Generalized or localized bone loss can occur from disuse, which is often a problem for those confined to a bed or a wheelchair, or for those who have an immobilized limb set in a cast or in traction.

The methods and compositions of the present invention are useful for treating and or preventing the following conditions or disease states: osteoporosis, which can include post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis; Paget's disease; abnormally increased bone turnover; periodontal disease; localized bone loss associated with periprosthetic osteolysis; and bone fractures.

The methods of the present invention are intended to specifically exclude methods for the treatment and/or prevention of prosthesis loosening and prosthesis migration in mammals as described in PCT application WO 95/30421, to Goodship et al, published Nov. 16, 1995, which is incorporated by reference herein in its entirety.

Bisphosphonates

The methods and compositions of the present invention comprise a bisphosphonate. The bisphosphonates of the present invention correspond to the chemical formula



wherein

A and X are independently selected from the group consisting of H, OH, halogen, NH_2, SH, phenyl, C1–C30 alkyl, C1–C30 substituted alkyl, C1–C10 alkyl or dialkyl substituted NH_2, C1–C10 alkoxy, C1–C10 alkyl or phenyl substituted thio, C1–C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1–C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH_2, C1–C10 alkyl or dialkyl substituted NH_2, OH, SH, and C1–C10 alkoxy.

In the foregoing chemical formula, A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Preferred structures are those in which A is selected from the group consisting of H, OH, and halogen, and X is selected from the group consisting of C1–C30 alkyl, C1–C30 substituted alkyl, halogen, and C1–C10 alkyl or phenyl substituted thio.

More preferred structures are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the group consisting of C1–C30 alkyl, C1–C30 substituted alkyl, Cl, and chlorophenylthio.

Most preferred is when A is OH and X is a 3-aminopropyl moiety, so that the resulting compound is a 4-amino-1,-hydroxybutylidene-1,1-bisphosphonate, i.e. alendronate.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C1–C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

"Pharmaceutically acceptable" as used herein means that the salts and derivatives of the bisphosphonates have the same general pharmacological properties as the free acid form from which they are derived and are acceptable from a toxicity viewpoint.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those or ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the

present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

Nonlimiting examples of bisphosphonates useful herein include the following:

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S. Pat. No. 4,922,007, to Kieczykowski et al., issued May 1, 1990, and U.S. Pat. No. 5,019,651, to Kieczykowski, issued May 28, 1991, both of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Pat. No. 4,970,335, to Isomura et al., issued Nov. 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Pat. No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Pat. No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Pat. No. 4,876,248, to Breliere et al., Oct. 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zolendronate).

Preferred are bisphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

More preferred is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

Most preferred is alendronate monosodium trihydrate.

Pharmaceutical Compositions

Compositions useful in the present invention comprise a pharmaceutically effective amount of a bisphosphonate. The bisphosphonate is typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers, collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups, effervescent compositions, powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs and syrups, effervescent compositions, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, buffers, coatings, and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such a glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is that described in U.S. Pat. No. 5,358,941, to Bechard et al, issued Oct. 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide, and the like.

The precise dosage of the bisphonate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 μg/kg body weight and preferably about 10 to about 2000 μg/kg of body weight.

For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis.

For once-weekly dosing, an oral unit dosage comprises from about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis Examples of weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

For twice-weekly dosing, an oral unit dosage comprises from about 8.75 mg to about 35 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of twice-weekly oral dosages include a unit

dosage which is useful for osteoporosis prevention comprising about 17.5 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 35 mg of the alendronate compound.

For biweekly or twice-monthly dosing, an oral unit dosage comprises from about 35 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of biweekly or twice-monthly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 70 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 140 mg of the alendronate compound.

Nonlimiting examples of oral compositions comprising alendronate, as well as other bisphosphonates, are illustrated in the Examples, below.

Sequential Administration Of Histamine H2 Receptor Blockers And/Or Proton Pump Inhibitors With Bisphosphonates

In further embodiments, the methods and compositions of the present invention can also comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H2 receptor blockers and proton pump inhibitors are well known therapeutic agents for increasing gastric pH. See L. J. Hixson, et al., *Current Trends in the Pharmacotherapy for Peptic Ulcer Disease, Arch. Intern. Med.,* vol. 152, pp. 726–732 (April 1992), which is incorporated by reference herein in its entirety. It is found in the present invention that the sequential oral administration of a histamine H2 receptor blocker and/or a proton pump inhibitor, followed by a bisphosphonate can help to further minimize adverse gastrointestinal effects. In these embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the bisphosphonate. In more preferred embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the bisphonate.

The dosage of the histamine H2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound selected and factors associated with the mammal to be treated, i.e. size, health, etc.

Nonlimiting examples of histamine H2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

Treatment Kits

In further embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium or dietary supplements, either in a form similar to or distinct from the bisphosphonate dosages, can be included to provide a kit in which a dosage is taken every day. In those embodiments including a histamine H2 receptor and/or proton pump inhibitor, these agents can be included as part of the kit.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the invention.

Example 1

Esophageal Irritation Potential

The esophageal irritation potential of the bisphosphonates is evaluated using a dog model.

The experiments demonstrate the relative irritation potential of the following dosing regimens: placebo (Group 1), a single high concentration dosage of alendronate monosodium trihydrate (Group 2), a low concentration dosage of alendronate monosodium trihydrate administered for five consecutive days (Groups 3 and 4), a high concentration dosage of alendronate monosodium trihydrate administered once per week for four weeks (Group 5), a mid-range concentration dosage of alendronate monosodium trihydrate administered twice per week for four weeks (Group 6), a low dosage of risedronate sodium administered for five consecutive days (Group 7), and a low dosage of tiludronate disodium administered for five consecutive days (Group 8).

The following solutions are prepared:

(1) simulated gastric juice (pH about 2), i.e. the control solution.

(2) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

(3) simulated gastric juice (pH about 2) containing about 0.80 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

(4) simulated gastric juice (pH about 2) containing about 0.40 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

(5) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of risedronate sodium on a risedronic acid active basis.

(6) simulated gastric juice (pH about 2) containing about 4.0 mg/mL of tiludronate disodium on a tiludronic acid active basis.

The simulated gastric juice is prepared by dissolving about 960 mg of pepsin (L-585,228000B003, Fisher Chemical) in about 147 mL of 0.90 (wt %) NaCl (aqueous), adding about 3 mL of 1.0 M HCl (aqueous), and adjusting the volume to about 300 mL with deionized water. The pH of the resulting solution is measured and if necessary is adjusted to about 2 using 1.0 M HCl (aqueous) or 1.0 M NaOH (aqueous).

The animals used in the experiments are anesthetized and administered about 50 mL of the appropriate solution over about 30 minutes by infusion into the esophagus using an infusion pump and a rubber catheter. The following treatment experiments are run:

Group 1: This control group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice [solution (1)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 2: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of alendronate [solution (2)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 3: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 24 hours after the dose is administered.

Group 4: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 7 days after the dose is administered.

Group 5: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] once per week, i.e. every seven days, for four weeks. The animals are administered a total of four dosages. The animals are sacrificed about 7 days after the last dose is administered.

Group 6: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.40 mg/mL of alendronate [solution (4)] twice per week, i.e. every three to four days, for four weeks. The animals are administered a total of eight dosages. The animals are sacrificed about four days after the last dose is administered.

Group 7: This group contains eight animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of risedronate [solution (5)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 8: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 4.0 mg/mL of tiludronate [solution (6)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

The esophagus from each sacrificed animal is removed and prepared for histopathology using standard techniques by embedding the tissue in paraffin, staining with hematoxylin and eosin. The sections are examined microscopically. The histopathology results are summarized in Table 1.

For the Group 1 animals (control group), the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. **1** is a representative photomicrograph from a Group 1 animal.

For the Group 2 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **2** is a representative photomicrograph from a Group 2 animal.

For the Group 3 animals, the photomicrographs show that the esophagus has an intact epithelial surface with very slight submucosal inflammation and vacuolation. FIG. **3** is a representative photomicrograph from a Group 3 animal.

For the Group 4 animals, the photomicrographs show that the esosphagus has an intact epithelium with either minimal inflammation (two of the five animals) or no inflammation (three of the five animals) and no vacuolation. FIG. **4** is a representative photomicrograph from a Group 4 animal exhibiting minimal inflammation.

For the Group 5 animals, the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. **5** is a representative photomicrograph from a Group 5 animal.

For the Group 6 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **6** is a representative photomicrograph from a Group 6 animal.

For the Group 7 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **7** is a representative photomicrograph from a Group 7 animal.

For the Group 8 animals, the photomicrographs show that the esophagus exhibits slight ulceration of the epithelial surface and slight submucosal inflammation and vacuolation. FIG. **8** is a representative photomicrograph from a Group 8 animal.

These experiments demonstrate that considerably less esophageal irritation (comparable to control Group 1) is observed from the administration of a single high concentration dosage of alendronate (Groups 3 and 4) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate consideraly less esophageal irritation is observed from the administration of a single high concentration of alendronate on a weekly basis (Group 5) or twice-weekly basis (Group 6) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate that when other bisphosphonates such as risedronate (Group 7) or tiludronate (Group 8) are administered at low dosages on consecutive days that the esophageal irritation potential is high.

TABLE 1

Esophageal Irritation Potential Studies

Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
1 (n = 4)	0	1× daily for 5 days	immediately after last dosing	Normal. Intact epithelium and absence of inflammatory cells in the submucosa.
2 (n = 4)	Alendronate 0.20	1× daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
3 (n = 5)	Alendronate 0.80	1×	24 hours after dosing	Intact epithelial surface with very slight submucosal inflammation and vacuolation.
4 (n = 5)	Alendronate 0.80	1×	7 days after dosing	Intact epithelium with either minimal inflammation (2 of 5 animals) or no inflammation (3 of 5 animals) and no vacuolation.
5 (n = 6)	Alendronate 0.80	1× weekly for a total of 4 doses	7 days after last dosing	Intact epithelium with no inflammation and no vacuolation.
6 (n = 6)	Alendronate 0.40	2× weekly for 4 weeks	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.

TABLE 1-continued

Esophageal Irritation Potential Studies

Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
7 (n = 8)	Risedronate 0.20	1× daily for 5 days	immediate ly after last dosing	Deep ulceration of epithelial surface (4 of 8 animals). Marked submucosal inflammation and vacuolation.
8 (n = 4)	Tiludronate 4.0	1× daily for 5 days	24 hours after last dosing	Slight submucosal inflammation and vacuolation (3 of 4 animals, including 1 of these animals with slight ulceration).

Example 2

Once-weekly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 3

Twice-weekly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 17.5 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 4

Biweekly dosing regimen

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 5

Twice-monthly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human twice-monthly, i.e. preferably about once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 6

In further embodiments, alendronate tablets or liquid formulations are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2–5, for treating or preventing other disorders associated with abnormal bone resorption.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2–5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

Example 7

Bisphosphonate tablets.

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Pat. No. 5,358,941, to Bechard et al., issued Oct. 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

Ingredient	Per Tablet	Per 4000 Tablets
Alendronate Monosodium Trihydrate	45.68mg	182.72g
Anhydrous Lactose, NF	71.32mg	285.28g
Microcrystalline Cellulose, NF	80.0 mg	320.0 g
Magnesium Stearate, NF	1.0 mg	4.0 g
Croscarmellose Sodium, NF	2.0 mg	8.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

Example 8

Liquid Bisphosphonate Formulation.

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients.

Ingredient	Weight
Alendronate Monosodium Trihydrate	91.35 mg
Sodium Propylparaben	22.5 mg
Sodium Butylparaben	7.5 mg
Sodium Citrate Dihydrate	1500 mg
Citric Acid Anhydrous	56.25 mg
Sodium Saccharin	7.5 mg
Water	qs 75 mL
1N Sodium Hydroxide (aq)	qs pH 6.75

The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g. about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

What is claimed is:

1. A method for inhibiting bone resorption in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

2. A method according to claim **1** wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

3. A method according to claim **2** wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

4. A method according to claim **3** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

5. A method according to claim **2** wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

6. A method according to claim **4** wherein said mammal is a human.

7. A method according to claim **6** wherein said dosing interval is once-weekly.

8. A method according to claim **7** wherein said unit dosage of said bisphosphonate comprises from about 17.5 mg to about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

9. A method according to claim **8** wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

10. A method according to claim **6** wherein said dosing interval is twice-weekly.

11. A method according to claim **10** wherein said unit dosage of said bisphosphonate comprises from about 8.75 mg to about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

12. A method according to claim **6** wherein said dosing interval is biweekly.

13. A method according to claim **12** wherein said unit dosage of said bisphosphonate comprises from about 35 mg to about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

14. A method according to claim **6** wherein said dosing interval is twice-monthly.

15. A method according to claim **14** wherein said unit dosage of said bisphosphonate comprises about 35 mg to about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

16. A method for treating osteoporosis in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting

of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

17. A method according to claim **16** wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

18. A method according to claim **17** wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

19. A method according to claim **18** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

20. A method according to claim **17** wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

21. A method according to claim **19** wherein said mammal is a human.

22. A method according to claim **21** wherein said dosing interval is once-weekly.

23. A method according to claim **22** wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

24. A method according to claim **21** wherein said dosing interval is twice-weekly.

25. A method according to claim **24** wherein said unit dosage of said bisphosphonate comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

26. A method according to claim **21** wherein said dosing interval is biweekly.

27. A method according to claim **26**, wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

28. A method according to claim **21** wherein said dosing interval is twice-monthly.

29. A method according to claim **28** wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

30. A method for preventing osteoporosis in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

31. A method according to claim **30** wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

32. A method according to claim **31** wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

33. A method according to claim **32** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

34. A method according to claim **31** wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

35. A method according to claim **33** wherein said mammal is a human.

36. A method according to claim **35** wherein said dosing interval is once-weekly.

37. A method according to claim **36** wherein said bisphosphonate unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

38. A method according to claim **35** wherein said dosing interval is twice-weekly.

39. A method according to claim **38** wherein said bisphosphonate unit dosage comprises about 17.5 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

40. A method according to claim **35** wherein said dosing interval is biweekly.

41. A method according to claim **40** wherein said bisphosphonate unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

42. A method according to claim **35** wherein said dosing interval is twice-monthly.

43. A method according to claim **42** wherein said bisphosphonate unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

44. A kit comprising at least one pharmaceutically effective unit dosage of a bisphosphonate for oral administration according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

* * * * *

EXHIBIT 8

US006015801A

United States Patent [19]

Daifotis et al.

[11] **Patent Number: 6,015,801**

[45] **Date of Patent: Jan. 18, 2000**

[54] **METHOD FOR INHIBITING BONE RESORPTION**

[75] Inventors: **Anastasia G. Daifotis**; **A. John Yates**, both of Westfield; **Arthur C. Santora, II**, Watchung, all of N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **09/134,215**

[22] Filed: **Aug. 14, 1998**

Related U.S. Application Data

[63] Continuation-in-part of application No. PCT/US98/14796, Jul. 17, 1998

[60] Provisional application No. 60/053,535, Jul. 23, 1997, and provisional application No. 60/053,351, Jul. 22, 1997.

[51] **Int. Cl.**[7] **A61K 31/66**

[52] **U.S. Cl.** **514/108**

[58] **Field of Search** 514/108

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Primary Examiner—Theodore J. Criares

Attorney, Agent, or Firm—Anthony D. Sabatelli; Melvin Winokur

[57] **ABSTRACT**

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for caring out the therapeutic methods disclosed herein.

59 Claims, 8 Drawing Sheets

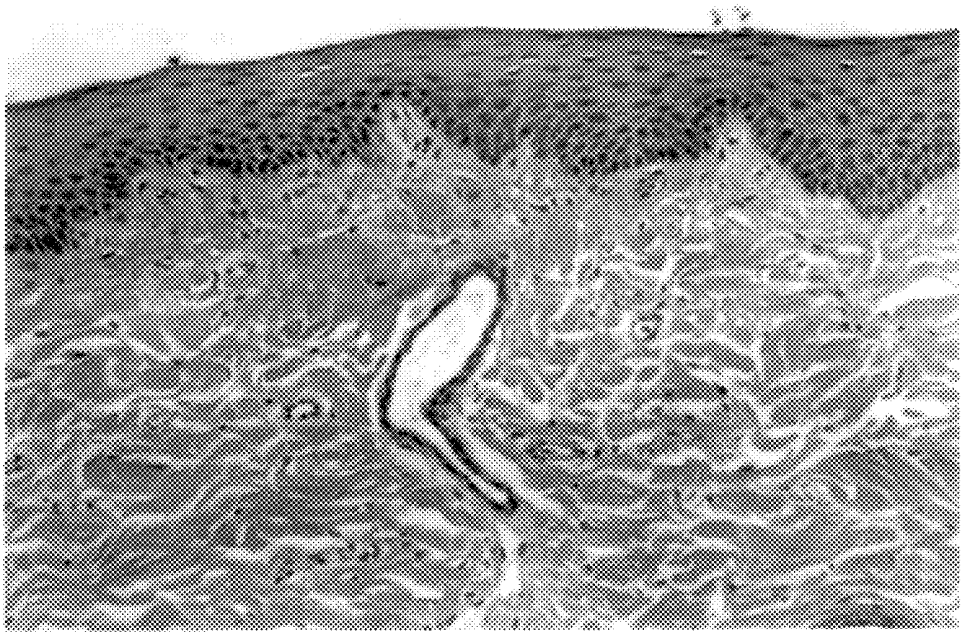
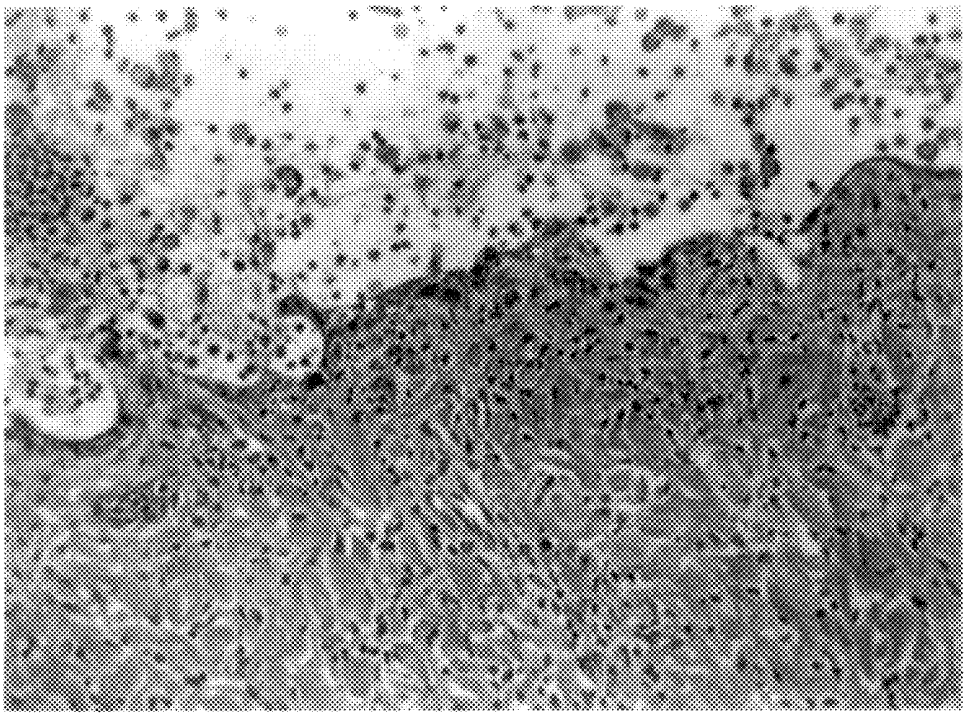


FIG. 1



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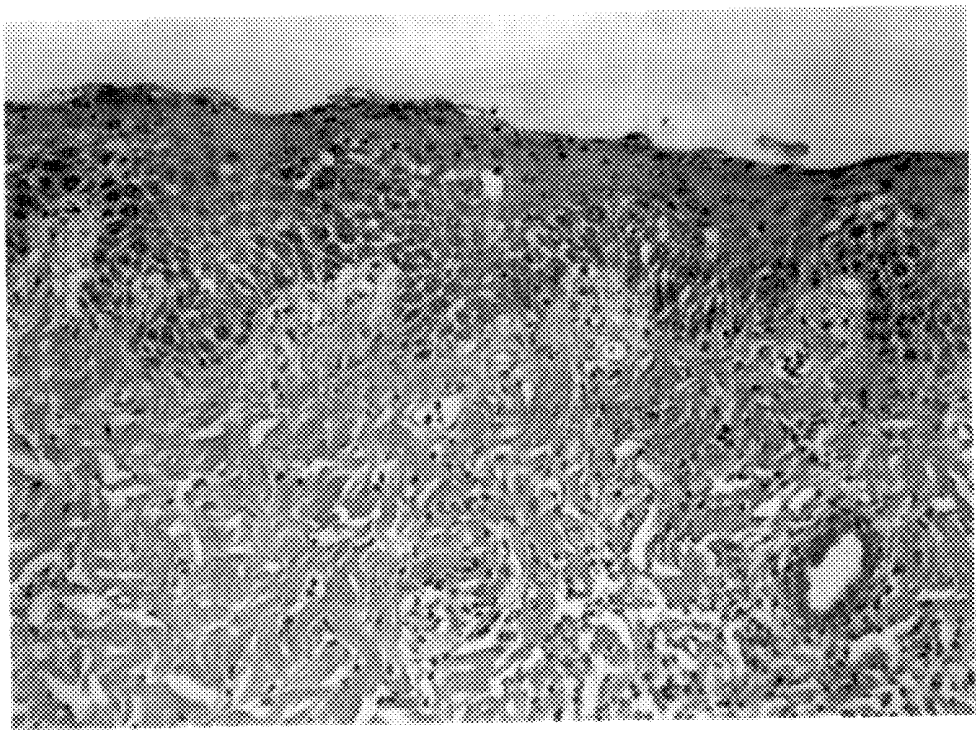

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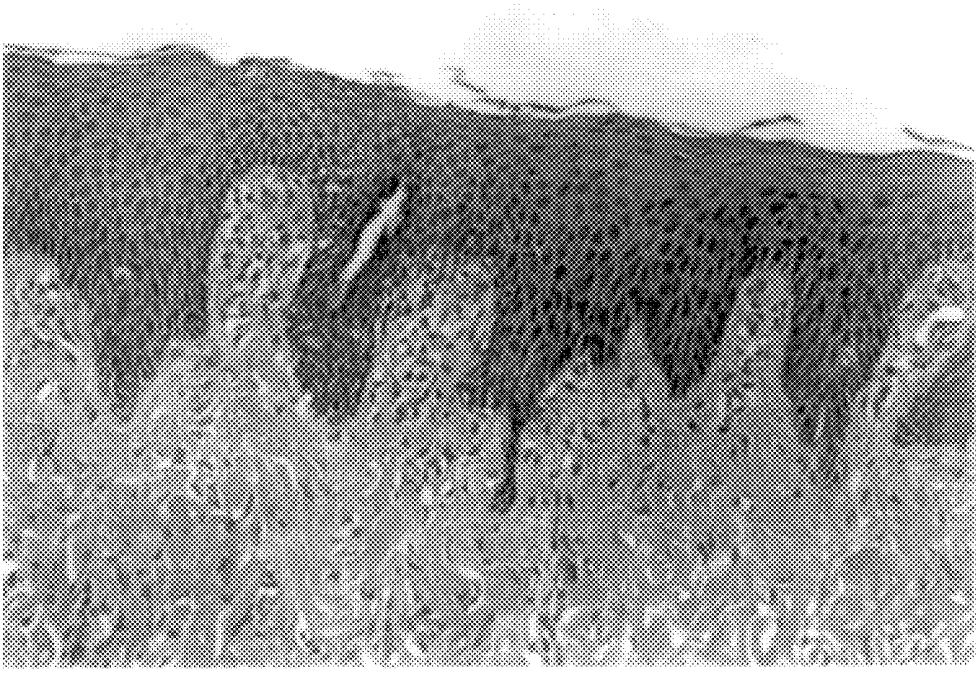

FIG.4

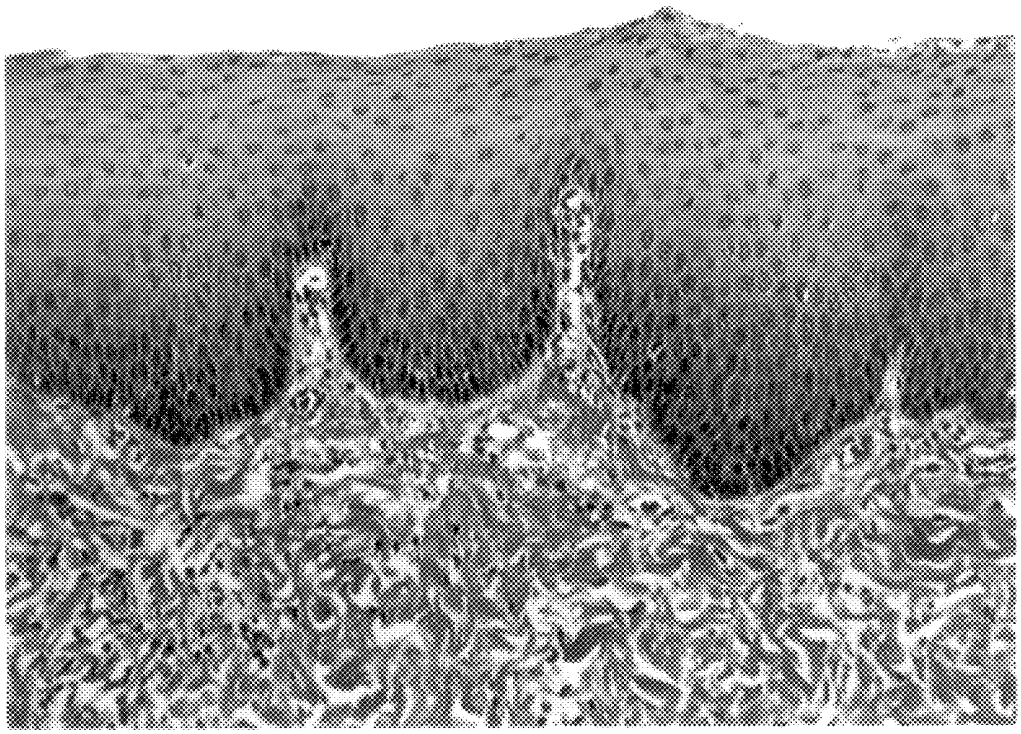

FIG. 5

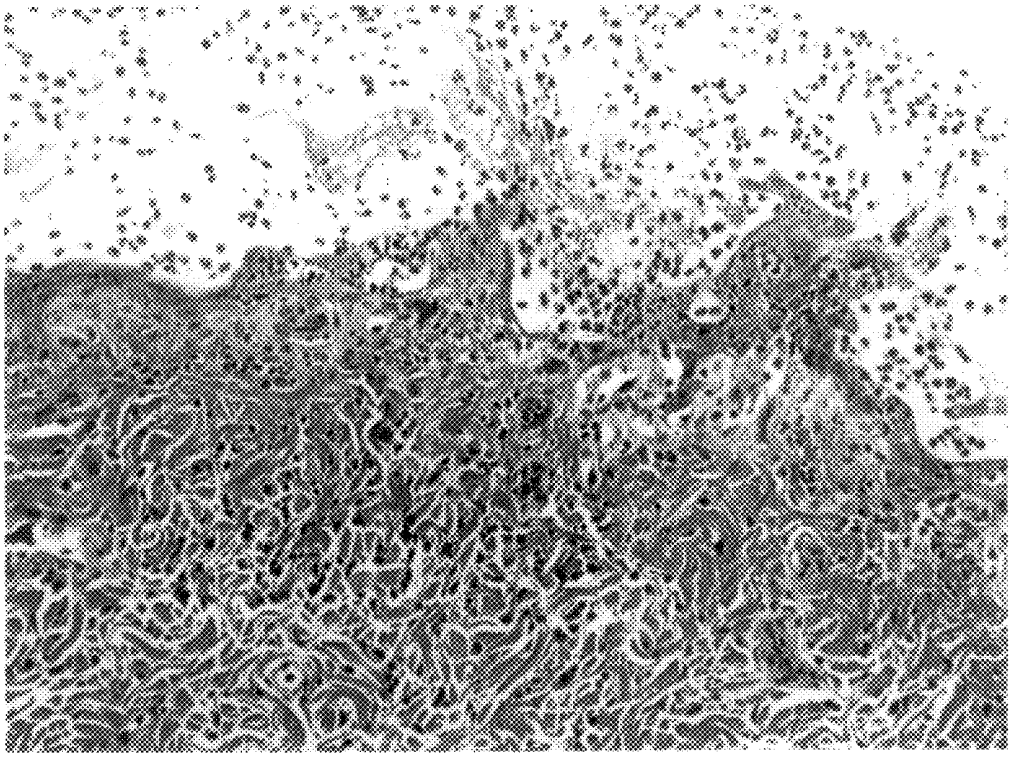

FIG.6

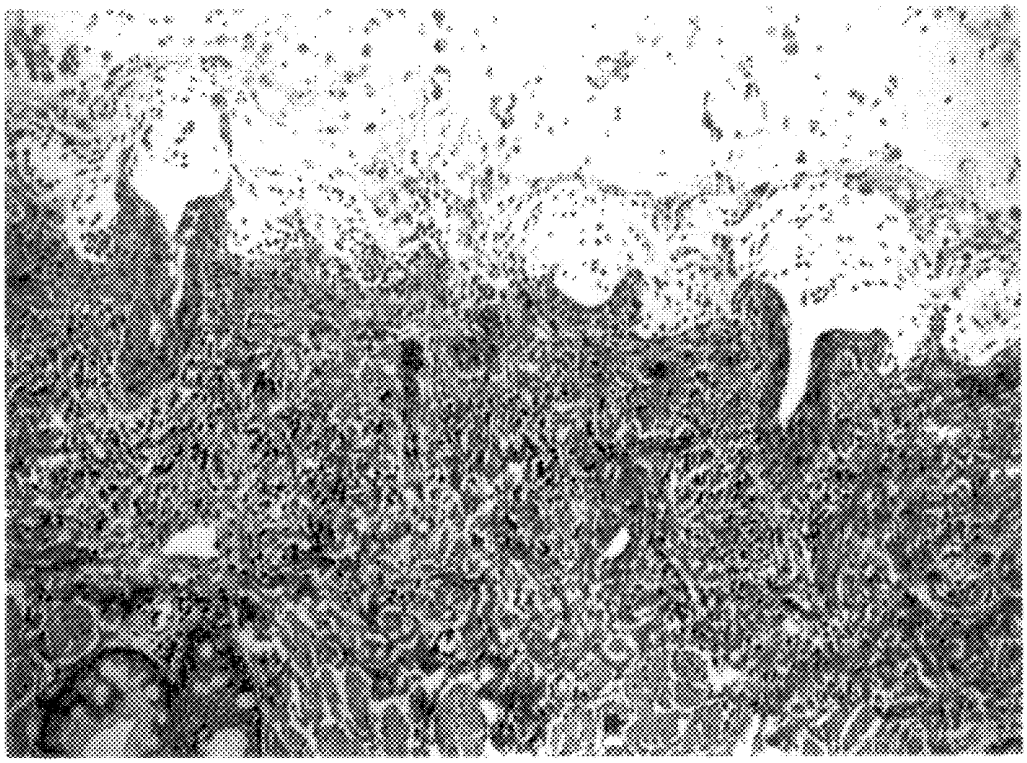

FIG. 7

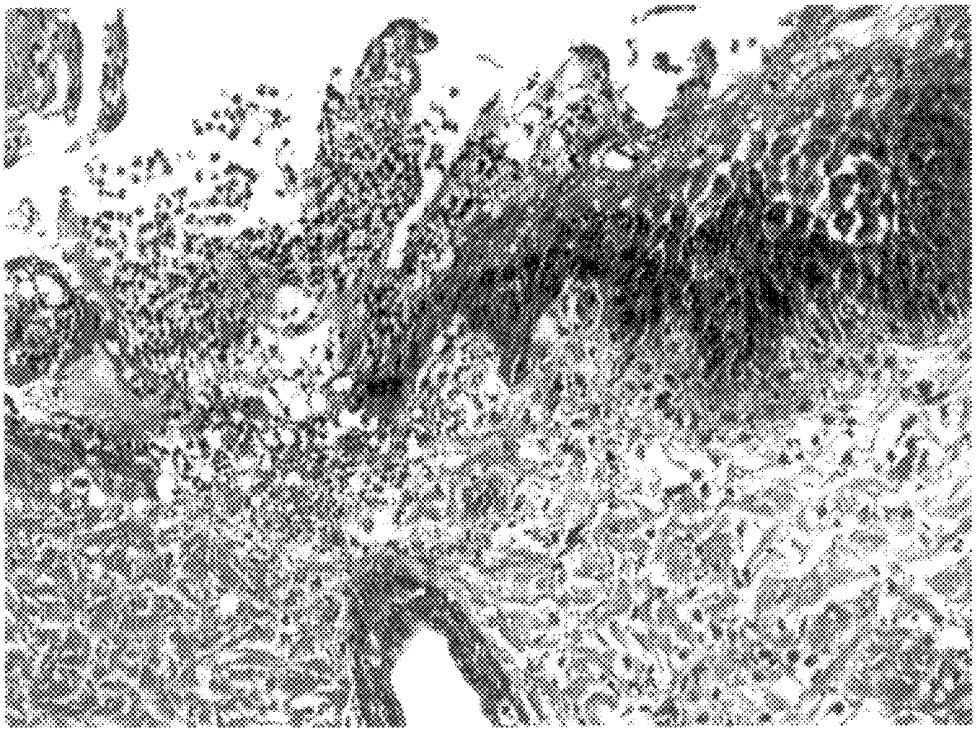

FIG.8

METHOD FOR INHIBITING BONE RESORPTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of PCT/US98/14796, filed Jul. 17, 1998, and also claims priority to U.S. provisional applications Ser. Nos. 60/053,535, filed Jul. 23, 1997, and 60/053,351, filed Jul. 22, 1997, both now abandoned, the contents of all of the foregoing of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to oral methods for inhibiting bone resorption in a mammal while minimizing the occurrence of or potential for adverse gastrointestinal effects. These methods comprise orally administering to a mammal in need thereof of a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. The present invention also relates to pharmaceutical compositions and kits useful for carrying out these methods.

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, metastatic bone disease, hypercalcemia of malignancy, multiple myeloma, periodontal disease, and tooth loss. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone disorders caused by or associated with abnormal bone resorption. See H. Fleisch, *Bisphosphonates In Bone Disease, From The Laboratory To The Patient,* 2nd Edition, Parthenon Publishing (1995), which is incorporated by reference herein in its entirety.

At present, a great amount of preclinical and clinical data exists for the potent bisphosphonate compound alendronate. Evidence suggests that other bisphosphonates such as risedronate, tiludronate, ibandronate and zolendronate, have many properties in common with alendronate, including high potency as inhibitors of osteoclastic bone resorption. An older bisphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent bisphosphonates, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization. See Boyce, B. F., Fogelman, I., Ralston, S. et al. (1984) Lancet 1(8381), pp. 821–824 (1984), and Gibbs, C.

J., Aaron, J. E.; Peacock, M. (1986) Br. Med. J. 292, pp. 1227–1229 (1986), both of which are incorporated by reference herein in their entirety.

Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. See B. J. Gertz et al., *Clinical Pharmacology of Alendronate Sodium, Osteoporosis Int.,* Suppl. 3: S13–16 (1993) and B. J. Gertz et al., *Studies of the oral bioavailability of alendronate, Clinical Pharmacology & Therapeutics,* vol. 58, number 3, pp. 288–298 (September, 1995), which are incorporated by reference herein in their entirety. Intravenous administration has been used to overcome this bioavailability problem. However, intravenous administration is costly and inconvenient, especially when the patient must be given an intravenous infusion lasting several hours on repeated occasions.

If oral administration of the bisphosphonate is desired, relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. To offset this low bioavailability, it is generally recommended that the patient take the bisphosphonate on an empty stomach and fast for at least 30 minutes afterwards. However, many patients find the need for such fasting on a daily basis to be inconvenient. Moreover, oral administration has been associated with adverse gastrointestinal effects, especially those relating to the esophagus. See Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate has been associated with esophageal ulcers. See E. G. Lufkin et al., *Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International,* 4: 320–322 (1994), which is incorporated by reference herein in its entirety. Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. See P. C. De Groen, et al., *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1016–1021 (1996), D. O. Castell, *Pill Esophagitis—The Case of Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1058–1059 (1996), and U. A. Liberman et al., *Esophagitis and Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1069–1070 (1996), which are incorporated by reference herein in their entirety. The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. See C. H. Chestnut et al., *Alendronate Treatment of the Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine,* vol. 99, pp. 144–152, (August, 1995), which is incorporated by reference herein in its entirety. Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fall into two categories: (1) those therapies utilizing continuous daily treatment, and (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

The continuous daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily dosing has the potential disadvantage of causing adverse gastrointestinal effects due to the repetitive, continuous, and

METHOD FOR INHIBITING BONE RESORPTION

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J., Aaron, J. E.; Peacock, M. (1986) Br. Med. J. 292, pp. 1227–1229 (1986), both of which are incorporated by reference herein in their entirety.

Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. See B. J. Gertz et al., *Clinical Pharmacology of Alendronate Sodium, Osteoporosis Int.,* Suppl. 3: S13–16 (1993) and B. J. Gertz et al., *Studies of the oral bioavailability of alendronate, Clinical Pharmacology & Therapeutics,* vol. 58, number 3, pp. 288–298 (September, 1995), which are incorporated by reference herein in their entirety. Intravenous administration has been used to overcome this bioavailability problem. However, intravenous administration is costly and inconvenient, especially when the patient must be given an intravenous infusion lasting several hours on repeated occasions.

If oral administration of the bisphosphonate is desired, relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. To offset this low bioavailability, it is generally recommended that the patient take the bisphosphonate on an empty stomach and fast for at least 30 minutes afterwards. However, many patients find the need for such fasting on a daily basis to be inconvenient. Moreover, oral administration has been associated with adverse gastrointestinal effects, especially those relating to the esophagus. See Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate has been associated with esophageal ulcers. See E. G. Lufkin et al., *Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International,* 4: 320–322 (1994), which is incorporated by reference herein in its entirety. Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. See P. C. De Groen, et al., *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1016–1021 (1996), D. O. Castell, *Pill Esophagitis—The Case of Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1058–1059 (1996), and U. A. Liberman et al., *Esophagitis and Alendronate, New England Journal of Medicine,* vol. 335, no. 124, pp. 1069–1070 (1996), which are incorporated by reference herein in their entirety. The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. See C. H. Chestnut et al., *Alendronate Treatment of the Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine,* vol. 99, pp. 144–152, (August, 1995), which is incorporated by reference herein in its entirety. Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fall into two categories: (1) those therapies utilizing continuous daily treatment, and (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

The continuous daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily dosing has the potential disadvantage of causing adverse gastrointestinal effects due to the repetitive, continuous, and

additive irritation to the gastrointestinal tract. Also, because bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

Cyclic treatment regimens were developed because some bisphosphonates, such as etidronate, when given daily for more than several days, have the disadvantage of actually causing a decline in bone mineralization, i.e. osteomalacia. U.S. Pat. No. 4,761,406, to Flora et al, issued Aug. 2, 1988, which is incorporated by reference herein in its entirety, describes a cyclic regimen developed in an attempt to minimize the decline in bone mineralization while still providing a therapeutic anti-resorptive effect. Generally, cyclic regimens are characterized as being intermittent, as opposed to continuous treatment regimens, and have both treatment periods during which the bisphosphonate is administered and nontreatment periods to permit the systemic level of the bisphosphonate to return to baseline. However, the cyclic regimens, relative to continuous dosing, appear to result in a decreased therapeutic antiresorptive efficacy. Data on risedronate suggests that cyclic dosing is actually less effective than continuous daily dosing for maximizing antiresorptive bone effects. See L. Mortensen, et al., *Prevention Of Early Postmenopausal Bone Loss By Risedronate, Journal of Bone and Mineral Research,* vol. 10, supp. 1, p. s140 (1995), which is incorporated by reference herein in its entirety. Furthermore, these cyclic regimens do not eliminate or minimize adverse gastrointestinal effects, because such regimens typically utilize periods of multiple daily dosing. Also, the cyclic regimens are cumbersome to administer and have the disadvantage of low patient compliance, and consequently compromised therapeutic efficacy. U.S. Pat. No. 5,366,965, to Strein, issued Nov. 22, 1994, which is incorporated by reference herein in its entirety, attempts to address the problem of adverse gastrointestinal effects by administering a polyphosphonate compound, either orally, subcutaneously, or intravenously, according to an intermittent dosing schedule having both a bone resorption inhibition period and a no-treatment rest period. However, the regimen has the disadvantage of not being continuous and regular, and requires nontreatment periods ranging from 20 to 120 days. PCT Application No. WO 95/30421, to Goodship et al, published Nov. 16, 1995, which is incorporated by reference herein in its entirety, discloses methods for preventing prosthetic loosening and migration using various bisphosphonate compounds. Administration of a once weekly partial dose of the bisphosphonate is disclosed. However, the reference specifically fails to address the issue of adverse gastrointestinal effects or to disclose administration of larger or multiple dosages.

It is seen from current teachings that both daily and cyclic treatment regimens have shortcomings, and that there is a need for development of a dosing regimen to overcome these shortcomings.

In the present invention, it is found that the adverse gastrointestinal effects that can be associated with daily or cyclic dosing regimens can be minimized by administering the bisphosphonate at a relatively high unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other words, it is found that the administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency. This result is surprising in view of the teachings suggesting that adverse gastrointestinal effects would be expected to increase as a function of increasing bisphosphonate dosage. Such administration methods of the present invention would be especially beneficial in treating patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing. Also, patients would not need to keep track of a complex dosing regimen. The methods of the present invention are likely to have the advantage of promoting better patient compliance, which in turn can translate into better therapeutic efficacy.

It is an object of the present invention to provide methods for inhibiting bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods for treating abnormal bone resorption and the conditions associated therewith

It is another object of the present invention to provide methods for preventing abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods which are oral methods.

It is another object of the present invention to provide such methods in humans.

It is another object of the present invention to provide such methods in patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders.

It is another object of the present invention to provide such methods while minimizing the occurrence of or potential for adverse gastronintestinal effects.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing interval selected from the group consisting of weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

It is another object of the present invention to provide such methods wherein the continuous dosing schedule is maintained until the desired therapeutic effect is achieved.

It is another object of the present invention to treat or prevent abnormal bone resorption in an osteoporotic mammal, preferably an osteoporotic human.

It is another object of the present invention to provide pharmaceutical compositions and kits useful in the methods herein.

These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to methods for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing, wherein said continuous schedule is maintained until the desired therapeutic effect is achieved for said mammal.

In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

In other embodiments, the present invention relates to methods for treating abnormal bone resorption in a mammal in need of such treatment.

In other embodiments, the present invention relates to methods for preventing abnormal bone resorption in a mammal in need of such prevention.

In other embodiments, the present invention relates to such methods useful in humans.

In other embodiments, the present invention relates to such methods useful in humans identified as having or being susceptible to upper gastrointestinal disorders.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a mammal.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a human.

In other embodiments, the present invention relates to methods for inhibiting bone resorption, or treating or preventing abnormal bone resorption in a human comprising administering to said human from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

In other embodiments the present invention relates to a pharmaceutical composition comprising from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

In other embodiments the present invention relates to a method for treating a condition or disease state in a mammal in need thereof selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

In other embodiments the present invention relates to a method for preventing a condition or disease state in a mammal in need thereof selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

All percentages and ratios used herein, unless otherwise indicated, are by weight. The invention hereof can comprise, consist of, or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of simulated gastric juice administered on five consecutive days.

FIG. **2** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/ml alendronate in simulated gastric juice administered on five consecutive days.

FIG. **3** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. **4** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. **5** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion of the last of 4 separate dosages of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice administered once per week, i.e. once every 7 days.

FIG. **6** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 4 days after infusion of the last of 8 separate dosages of 50 mL of 0.40 mg/mL alendronate in simulated gastric juice administered twice per week, i.e. once every 3–4 days.

FIG. **7** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL risedronate in simulated gastric juice administered on five consecutive days.

FIG. **8** is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 4.0 mg/mL tiludronate in simulated gastric juice administered on five consecutive days.

DESCRIPTION OF THE INVENTION

The present invention relates to a method, preferably an oral method, for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects. The present invention relates to methods of treating or preventing abnormal

bone resorption in a mammal in need of such treatment or prevention. The methods of the present invention comprise orally administering to a mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage, wherein said dosage is administered according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days. Typically, the continuous dosing schedule is maintained until the desired therapeutic effect is achieved for the mammal.

The present invention utilizes higher unit dosages of the bisphosphonate at each dosing point than has heretofore been typically administered, yet because of the dosing schedule chosen, the potential for adverse gastrointestinal effects are minimized. Moreover, the method is more convenient because the disadvantages associated with daily dosing are minimized.

The methods of the present invention are generally administered to mammals in need of bisphosphonate therapy. Preferably the mammals are human patients, particularly human patients in need of inhibiting bone resorption, such as patients in need of treating or preventing abnormal bone resorption.

The administration methods of the present invention are especially useful in administering bisphosphonate therapy to human patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. GERD, esophagitis, dyspepsia, ulcers, etc. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

The term "pharmaceutically effective amount", as used herein, means that amount of the bisphosphonate compound, that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the bisphosphonate is a bone resorption inhibiting amount.

The term "minimize the occurrence of or potential for adverse gastrointestinal effects", as used herein, means reducing, preventing, decreasing, or lessening the occurrence of or the potential for incurring unwanted side effects in the gastrointestinal tract, i.e. the esophagus, stomach, intestines, and rectum, particularly the upper gastrointestinal tract, i.e. the esophagus and stomach. Nonlimiting adverse gastrointestinal effects include, but are not limited to GERD, esophagitis, dyspepsia, ulcers, esophageal irritation, esophageal perforation, abdominal pain, and constipation.

The term "abnormal bone resorption", as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. Alternatively, "abnormal bone resorption" can be associated with the formation of bone having an abnormal structure.

The term "bone resorption inhibiting", as used herein, means treating or preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to treatment or prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

The terms "continuous schedule" or "continuous dosing schedule", as used herein, mean that the dosing regimen is repeated until the desired therapeutic effect is achieved. The continuous schedule or continuous dosing schedule is distinguished from cyclical or intermittent administration.

The term "until the desired therapeutic effect is achieved", as used herein, means that the bisphosphonate compound is continuously administered, according to the dosing schedule chosen, up to the time that the clinical or medical effect sought for the disease or condition is observed by the clinician or researcher. For methods of treatment of the present invention, the bisphosphonate compound is continuously administered until the desired change in bone mass or structure is observed. In such instances, achieving an increase in bone mass or a replacement of abnormal bone structure with more normal bone structure are the desired objectives. For methods of prevention of the present invention, the bisphosphonate compound is continuously administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of bone mass density is often the objective. Nonlimiting examples of administration periods can range from about 2 weeks to the remaining lifespan of the mammal. For humans, administration periods can range from about 2 weeks to the remaining lifespan of the human, preferably from about 2 weeks to about 20 years, more preferably from about 1 month to about 20 years, more preferably from about 6 months to about 10 years, and most preferably from about 1 year to about 10 years.

Methods of the Present Invention

The present invention comprises methods for inhibiting bone resorption in mammals. The present invention also comprises treating abnormal bone resorption in mammals. The present invention also comprises methods for preventing abnormal bone resorption in mammals. In preferred embodiments of the present invention, the mammal is a human.

The methods of the present invention do not have the disadvantages of current methods of treatment which can cause or increase the potential for adverse gastrointestinal effects or which require cumbersome, irregular, or complicated dosing regimens.

The present invention comprises a continuous dosing schedule whereby a unit dosage of the bisphosphonate is regularly administered according to a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

By once-weekly dosing is meant that a unit dosage of the bisphosphonate is administered once a week, i.e. one time during a seven day period, preferably on the same day of each week. In the once-weekly dosing regimen, the unit dosage is generally administered about every seven days. A nonlimiting example of a once-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the once-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days falling within two different weekly periods.

By twice-weekly dosing is meant that a unit dosage of the bisphosphonate is administered twice a week; i.e. two times during a seven day period, preferably on the same two days of each weekly period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every three to four days. A nonlimiting example of a twice-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday and Wednesday. It is preferred that the unit dosages are not administered on

the same or consecutive days, but the twice-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days within a weekly period or different weekly periods.

By biweekly dosing is meant that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every fourteen days. A nonlimiting example of a biweekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period, or different monthly periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens have a different periodicity and result in the administration of different numbers of dosages over long periods of time. For example, over a one year period, a total of about twenty four dosages would be administered according to the twice-monthly regimen (because there are twelve calendar months in a year), whereas a total of about twenty six dosages would be administered according to the biweekly dosing regimen (because there are about fifty-two weeks in a year).

In further embodiments or descriptions of the present invention, the unit dosage is given with a periodicity ranging from about once every 3 days to about once every 16 days.

The methods and compositions of the present invention are useful for inhibiting bone resorption and for treating and preventing abnormal bone resorption and conditions associated therewith. Such conditions include both generalized and localized bone loss. Also, the creation of bone having an abnormal structure, as in Paget's disease, can be associated with abnormal bone resorption.

The methods and compositions of the present invention are also useful for treating and preventing conditions such as metastatic bone disease, hypercalcemia of malignancy, multiple myeloma, periodontal disease, and tooth loss. Metastatic bone disease involves tumor-induced skeletal metastases which commonly result from breast cancer, prostate cancer, lung cancer, renal cancer, thyroid cancer, and multiple myeloma. The most frequent clinical manifestations of bone metastases are pain, pathological fracture, immobility, nerve root or spinal cord compression, hypercalcemia, and compromised hematopoiesis. Hypercalcemia of malignancy is also tumor-induced. It is characterized by high levels of serum calcium and is often associated with metastatic bone disease, particularly with non-ambulatory patients. Multiple myeloma is a primary tumor of the bone marrow cells. See U.S. Pat. No. 5,780,455, to Brenner et al., issued Jul. 14, 1998, which is incorporated by reference herein in its entirety.

The term "generalized bone loss" means bone loss at multiple skeletal sites or throughout the skeletal system. The term "localized bone loss" means bone loss at one or more specific, defined skeletal sites.

Generalized boss loss is often associated with osteoporosis. Osteoporosis is most common in post-menopausal women, wherein estrogen production has been greatly diminished. However, osteoporosis can also be steroid-induced and has been observed in males due to age. Osteoporosis can be induced by disease, e.g. rheumatoid arthritis, it can be induced by secondary causes, e.g., glucocorticoid therapy, or it can come about with no identifiable cause, i.e. idiopathic osteoporosis. In the present invention, preferred methods include the treatment or prevention of abnormal bone resorption in osteoporotic humans.

Localized bone loss has been associated with periodontal disease, with bone fractures, and with periprosthetic osteolysis (in other words where bone resorption has occurred in proximity to a prosthetic implant).

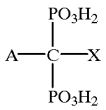
Generalized or localized bone loss can occur from disuse, which is often a problem for those confined to a bed or a wheelchair, or for those who have an immobilized limb set in a cast or in traction.

The methods and compositions of the present invention are useful for treating and or preventing the following conditions or disease states: osteoporosis, which can include post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis; Paget's disease; abnormally increased bone turnover; periodontal disease; tooth loss; localized bone loss associated with periprosthetic osteolysis; bone fractures; metastatic bone disease; hypercalcemia of malignancy; and multiple myeloma.

The methods of the present invention are intended to specifically exclude methods for the treatment and/or prevention of prosthesis loosening and prosthesis migration in mammals as described in PCT application WO 95/30421, to Goodship et al, published Nov. 16, 1995, which is incorporated by reference herein in its entirety.

Bisphosphonates

The methods and compositions of the present invention comprise a bisphosphonate. The bisphosphonates of the present invention correspond to the chemical formula



wherein

A and X are independently selected from the group consisting of H, OH, halogen, NH_2, SH, phenyl, C1–C30 alkyl, C1–C30 substituted alkyl, C1–C10 alkyl or dialkyl substituted NH_2, C1–C10 alkoxy, C1–C10 alkyl or phenyl substituted thio, C1 –C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1–C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH_2, C1–C10 alkyl or dialkyl substituted NH_2, OH, SH, and C1–C10 alkoxy.

In the foregoing chemical formula, A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantly, and chlorophenylthio.

Preferred structures are those in which A is selected from the group consisting of H, OH, and halogen, and X is selected from the group consisting of C1–C30 alkyl, C1–C30 substituted alkyl, halogen, and C1–C10 alkyl or phenyl substituted thio.

More preferred structures are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the group consisting of C1–C30 alkyl, C1–C30 substituted alkyl, Cl, and chlorophenylthio.

Most preferred is when A is OH and X is a 3-aminopropyl moiety, so that the resulting compound is a 4-amino-1,-hydroxybutylidene-1,1-bisphosphonate, i.e. alendronate.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C1–C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

"Pharmaceutically acceptable" as used herein means that the salts and derivatives of the bisphosphonates have the same general pharmacological properties as the free acid form from which they are derived and are acceptable from a toxicity viewpoint.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those or ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

Nonlimiting examples of bisphosphonates useful herein include the following:

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S. Pat. No. 4,922,007, to Kieczykowski et al., issued May 1, 1990, and U.S. Pat. No. 5,019,651, to Kieczykowski, issued May 28, 1991, both of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Pat. No. 4,970,335, to Isomura et al., issued Nov. 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Pat. No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]- 1,1 -bisphosphonic acid (piridronate) is described in U.S. Pat. No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Pat. No. 4,876,248, to Breliere et al., Oct. 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zolendronate).

Preferred are bisphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

More preferred is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

Most preferred is alendronate monosodium trihydrate.

Pharmaceutical Compositions

Compositions useful in the present invention comprise a pharmaceutically effective amount of a bisphosphonate. The bisphosphonate is typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers, collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups, effervescent compositions, powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs, syrups, and effervescent compositions, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, buffers, coatings, flavoring agents, and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such a glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and

the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is that described in U.S. Pat. No. 5,358,941, to Bechard et al, issued Oct. 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropyl-methacrylamide, and the like.

The precise dosage of the bisphonate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 μg/kg body weight and preferably about 10 to about 2000 μg/kg of body weight.

For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis.

For once-weekly dosing, an oral unit dosage comprises from about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

For twice-weekly dosing, an oral unit dosage comprises from about 8.75 mg to about 35 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of twice-weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 17.5 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 35 mg of the alendronate compound.

For biweekly or twice-monthly dosing, an oral unit dosage comprises from about 35 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of biweekly or twice-monthly oral dosages include a unit dosage which is useful for useful for osteoporosis prevention comprising about 70 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 140 mg of the alendronate compound.

Nonlimiting examples of oral compositions comprising alendronate, as well as other bisphosphonates, are illustrated in the Examples, below.

Sequential Administration of Histamine H2 Receptor Blockers and/or Proton Pump Inhibitors with Bisphosphonates

In further embodiments, the methods and compositions of the present invention can also comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H2 receptor blockers and proton pump inhibitors are well known therapeutic agents for increasing gastric pH. See L. J. Hixson, et al., *Current Trends in the Pharmacotherapy for Peptic Ulcer Disease, Arch. Intern. Med.,* vol. 152, pp. 726–732 (April, 1992), which is incorporated by reference herein in its entirety. It is found in the present invention that the sequential oral administration of a histamine H2 receptor blocker and/or a proton pump inhibitor, followed by a bisphosphonate can help to further minimize adverse gastrointestinal effects. In these embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the bisphosphonate. In more preferred embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the bisphonate.

The dosage of the histamine H2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound selected and factors associated with the mammal to be treated, i.e. size, health, etc.

Nonlimiting examples of histamine H2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omprazole, and lansoprazole.

Treatment Kits

In further embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium or dietary supplements, either in a form similar to or distinct from the bisphosphonate dosages, can be included to provide a kit in which a dosage is taken every day. In those embodiments including a histamine H2 receptor and/or proton pump inhibitor, these agents can be included as part of the kit.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the invention.

Example 1

Esophageal Irritation Potential

The esophageal irritation potential of the bisphosphonates is evaluated using a dog model.

The experiments demonstrate the relative irritation potential of the following dosing regimens: placebo (Group 1), a single high concentration dosage of alendronate monosodium trihydrate (Group 2), a low concentration dosage of alendronate monosodium trihydrate administered for five consecutive days (Groups 3 and 4), a high concentration dosage of alendronate monosodium trihydrate administered once per week for four weeks (Group 5), a mid-range concentration dosage of alendronate monosodium trihydrate

administered twice per week for four weeks (Group 6), a low dosage of risedronate sodium administered for five consecutive days (Group 7), and a low dosage of tiludronate disodium administered for five consecutive days (Group 8).

The following solutions are prepared:

(1) simulated gastric juice (pH about 2), i.e. the control solution.

(2) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

(3) simulated gastric juice (pH about 2) containing about 0.80 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

(4) simulated gastricjuice (pH about 2) containing about 0.40 mg/mL of alendronate monosodium trihydrate on an alendronic add active basis.

(5) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of risedronate sodium on a risedronic acid active basis.

(6) simulated gastric juice (pH about 2) containing about 4.0 mg/mL of tiludronate disodium on a tiludronic acid active basis.

The simulated gastric juice is prepared by dissolving about 960 mg of pepsin (L-585,228000B003, Fisher Chemical) in about 147 mL of 0.90 (wt %) NaCl (aqueous), adding about 3 mL of 1.0 M HCl (aqueous), and adjusting the volume to about 300 mL with deionized water. The pH of the resulting solution is measured and if necessary is adjusted to about 2 using 1.0 M HCl (aqueous) or 1.0 M NaOH (aqueous).

The animals used in the experiments are anesthetized and administered about 50 mL of the appropriate solution over about 30 minutes by infusion into the esophagus using an infusion pump and a rubber catheter. The following treatment experiments are run:

Group 1: This control group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice [solution (1)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 2: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of alendronate [solution (2)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 3: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 24 hours after the dose is administered.

Group 4: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 7 days after the dose is administered.

Group 5: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] once per week, i.e. every seven days, for four weeks. The animals are administered a total of four dosages. The animals are sacrificed about 7 days after the last dose is administered.

Group 6: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.40 mg/mL of alendronate [solution (4)] twice per week, i.e. every three to four days, for four weeks. The animals are administered a total of eight dosages. The animals are sacrificed about four days after the last dose is administered.

Group 7: This group contains eight animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of risedronate [solution (5)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 8: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 4.0 mg/mL of tiludronate [solution (6)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

The esophagus from each sacrificed animal is removed and prepared for histopathology using standard techniques by embedding the tissue in paraffin, staining with hematoxylin and eosin. The sections are examined microscopically. The histopathology results are summarized in Table 1.

For the Group 1 animals (control group), the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. **1** is a representative photomicrograph from a Group 1 animal.

For the Group 2 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **2** is a representative photomicrograph from a Group 2 animal.

For the Group 3 animals, the photomicrographs show that the esophagus has an intact epithelial surface with very slight submucosal inflammation and vacuolation. FIG. **3** is a representative photomicrograph from a Group 3 animal.

For the Group 4 animals, the photomicrographs show that the esosphagus has an intact epithelium with either minimal inflammation (two of the five animals) or no inflammation (three of the five animals) and no vacuolation. FIG. **4** is a representative photomicrograph from a Group 4 animal exhibiting minimal inflammation.

For the Group 5 animals, the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. **5** is a representative photomicrograph from a Group 5 animal.

For the Group 6 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **6** is a representative photomicrograph from a Group 6 animal.

For the Group 7 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **7** is a representative photomicrograph from a Group 7 animal.

For the Group 8 animals, the photomicrographs show that the esophagus exhibits slight ulceration of the epithelial surface and slight submucosal inflammation and vacuolation. FIG. **8** is a representative photomicrograph from a Group 8 animal.

These experiments demonstrate that considerably less esophageal irritation (comparable to control Group 1)is observed from the administration of a single high concentration dosage of alendronate (Groups 3 and 4) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate con-

siderably less esophageal irritation is observed from the administration of a single high concentration of alendronate on a weekly basis (Group 5) or twice-weekly basis (Group 6) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate that when other bisphosphonates such as risedronate (Group 7) or tiludronate (Group 8) are administered at low dosages on consecutive days that the esophageal irritation potential is high.

TABLE 1

Esophageal Irritation Potential Studies

Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
1 (n = 4)	0	1× daily for 5 days	immediately after last dosing	Normal. Intact epithelium and absence of inflammatory cells in the submucosa.
2 (n = 4)	Alendronate 0.20	1× daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
3 (n = 5)	Alendronate 0.80	1×	24 hours after dosing	Intact epiffielial surface with very slight submucosal inflammation and vacuolation.
4 (n = 5)	Alendronate 0.80	1×	7 days after dosing	Intact epitheliwn with either minimal inflammation (2 of 5 animals) or no inflammation (3 of 5 animals) and no vacuolation.
5 (n = 6)	Alendronate 0.80	1× weekly for a total of 4 doses	7 days after dosing	Intact epithelium last with no inflammation and no vacuolation.
6 (n = 6)	Alendronate 0.40	2× weekly for 4 weeks	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
7 (n = 8)	Risedronate 0.20	1× daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface (4 of 8 animals). Marked submucosal inflammation and vacuolation.
8 (n = 4)	Tiludronate 4.0	1× daily for 5 days	24 hours after last dosing	Slight submucosal inflammation and vacuolation (3 of 4 animals, including 1 of these animals with slight ulceration).

Example 2

Once-Weekly Dosing Regimen

Treatment of Osteoporosis

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 3

Twice-Weekly Dosing Regimen

Treatment of Osteoporosis

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis

Alendronate tablets or liquid formulations containing about 17.5 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 4

Biweekly Dosing Regimen

Treatment of Osteoporosis

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 5

Twice-Monthly Dosing Regimen

Treatment of Osteoporosis

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human twice-monthly, i.e. preferably about once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 6

In further embodiments, alendronate tablets or liquid formulations are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2–5, for treating or preventing other disorders associated with abnormal bone resorption.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2–5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

Example 7

Bisphosphonate Tablets

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Pat. No. 5,358,941, to Bechard et al., issued Oct. 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

Ingredient	Per Tablet	Per 4000 Tablets
Alendronate Monosodium Trihydrate	45.68 mg	182.72 g
Anhydrous Lactose, NF	71.32 mg	285.28 g
Microcrystalline Cellulose, NF	80.0 mg	320.0 g
Magnesium Stearate, NF	1.0 mg	4.0 g
Croscarmellose Sodium, NF	2.0 mg	8.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

Example 8

Liquid Bisphosphonate Formulation

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients.

Ingredient	Weight
Mendronate Monosodium Trihydrate	91.35 mg
Sodium Propylparaben	22.5 mg
Sodium Butylparaben	7.5 mg
Sodium Citrate Dihydrate	1500 mg
Citric Acid Anhydrous	56.25 mg
Sodium Saccharin	7.5 mg
Water	qs 75 mL
1 N Sodium Hydroxide (aq)	qs pH 6.75

The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g. about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

What is claimed is:

1. A method for treating a condition or disease state in a mammal, said disease state or condition selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

2. A method according to claim **1** wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

3. A method according to claim **2** wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

4. A method according to claim **3** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

5. A method according to claim 2 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

6. A method according to claim 4 wherein said mammal is a human.

7. A method according to claim 6 wherein said dosing interval is once-weekly.

8. A method according to claim 7 wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

9. A method according to claim 6 wherein said dosing interval is twice-weekly.

10. A method according to claim 8 wherein said unit dosage of said bisphosphonate comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

11. A method according to claim 6 wherein said dosing interval is biweekly.

12. A method according to claim 11 wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

13. A method according to claim 6 wherein said dosing interval is twice-monthly.

14. A method according to claim 13 wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

15. A method for preventing a condition or disease state in a mammal in need thereof, said disease state or condition selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

16. A method according to claim 15 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

17. A method according to claim 16 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

18. A method according to claim 17 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

19. A method according to claim 16 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

20. A method according to claim 18 wherein said mammal is a human.

21. A method according to claim 20 wherein said dosing interval is once-weekly.

22. A method according to claim 21 wherein said unit dosage of said bisphosphonate comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

23. A method according to claim 20 wherein said dosing interval is twice-weekly.

24. A method according to claim 23 wherein said unit dosage of said bisphosphonate comprises about 17.5 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

25. A method according to claim 20 wherein said dosing interval is biweekly.

26. A method according to claim 25 wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

27. A method according to claim 20 wherein said dosing interval is twice-monthly.

28. A method according to claim 27 wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

29. A method for treating a condition or disease state in a mammal, said disease state or condition selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 receptor blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

30. A method according to claim 21 wherein said histamine H2 blocker or said proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of said bisphosphonate.

31. A method according to claim 30 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

32. A method according to claim 31 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

33. A method according to claim 32 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

34. A method according to claim 31 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

35. A method according to claim 33 wherein said mammal is a human.

36. A method according to claim 35 wherein said dosing interval is once-weekly.

37. A method according to claim 36 wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

38. A method according to claim 35 wherein said dosing interval is twice-weekly.

39. A method according to claim 38 wherein said unit dosage of said bisphosphonate comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

40. A method according to claim 35 wherein said dosing interval is biweekly.

41. A method according to claim **39** wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

42. A method according to claim **35** wherein said dosing interval is twice-monthly.

43. A method according to claim **42** wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

44. A method for preventing a condition or disease state in a mammal in need thereof, said disease state or condition selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 receptor blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

45. A method according to claim **44** wherein said histamine H2 receptor blocker or said proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of said bisphosphonate.

46. A method according to claim **45** wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

47. A method according to claim **46** wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

48. A method according to claim **47** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

49. A method according to claim **46** wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

50. A method according to claim **48** wherein said mammal is a human.

51. A method according to claim **50** wherein said dosing interval is once-weekly.

52. A method according to claim **51** wherein said bisphosphonate unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

53. A method according to claim **50** wherein said dosing interval is twice-weekly.

54. A method according to claim **53** wherein said bisphosphonate unit dosage comprises about 17.5 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

55. A method according to claim **50** wherein said dosing interval is biweekly.

56. A method according to claim **55** wherein said bisphosphonate unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

57. A method according to claim **50** wherein said dosing interval is twice-monthly.

58. A method according to claim **57** wherein said bisphosphonate unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

59. A method according to any one of claims **29–58** wherein said histamine H2 receptor blocker or proton pump inhibitor is selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omprazole, and lansoprazole.

* * * * *

EXHIBIT 9

US006225294B1

(12) **United States Patent**
Daifotis et al.

(10) **Patent No.: US 6,225,294 B1**
(45) **Date of Patent: May 1, 2001**

(54) **METHOD FOR INHIBITING BONE RESORPTION**

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(73) Assignee: **Merck & Co., Inc.**, Rahway, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/440,577**

(22) Filed: **Nov. 15, 1999**

Related U.S. Application Data

(63) Continuation of application No. 09/134,214, filed on Aug. 14, 1998, now Pat. No. 5,994,329, which is a continuation of application No. PCT/US98/14796, filed on Jul. 17, 1998.
(60) Provisional application No. 60/053,535, filed on Jul. 23, 1997, and provisional application No. 60/053,351, filed on Jul. 22, 1997.

(51) **Int. Cl.**[7] **A61K 31/66**

(52) **U.S. Cl.** **514/108**

(58) **Field of Search** 514/108

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(74) *Attorney, Agent, or Firm*—Anthony D. Sabatelli; Melvin Winokur

(57) **ABSTRACT**

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein.

94 Claims, 8 Drawing Sheets

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FIG. 1

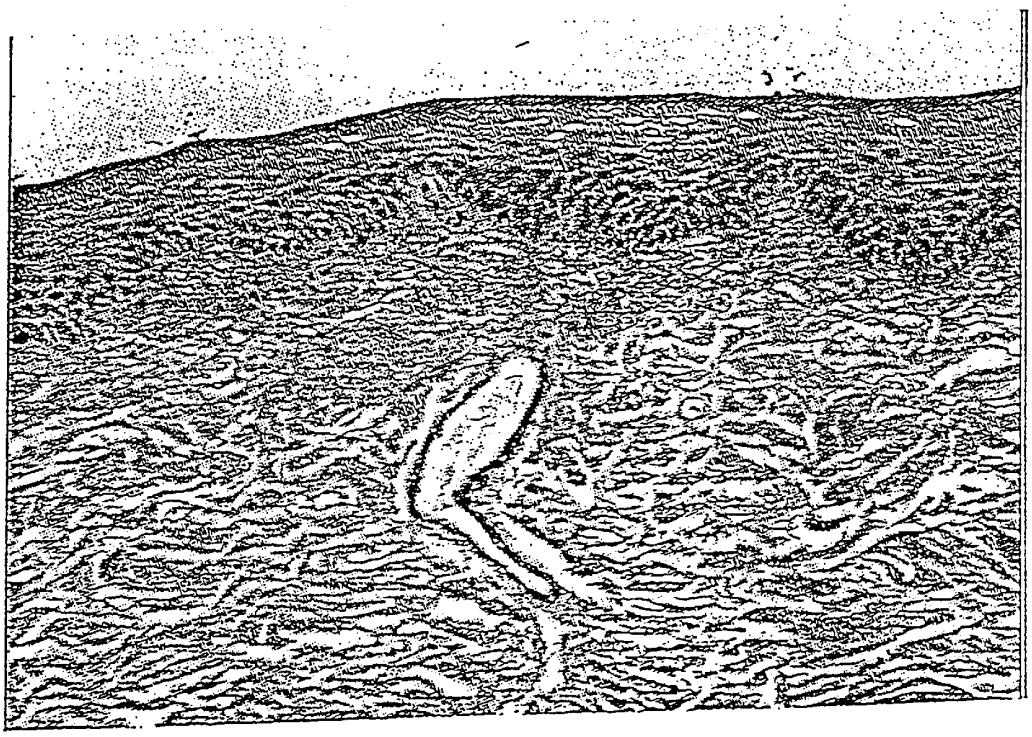


FIG. 2

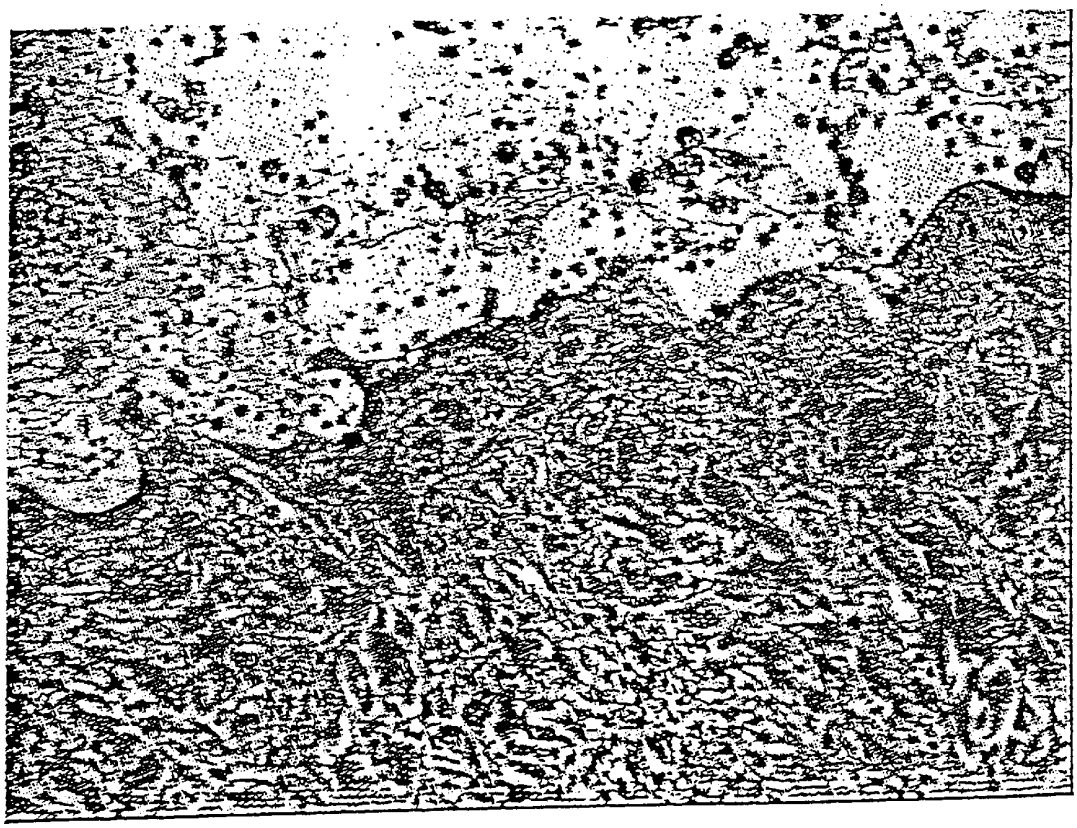
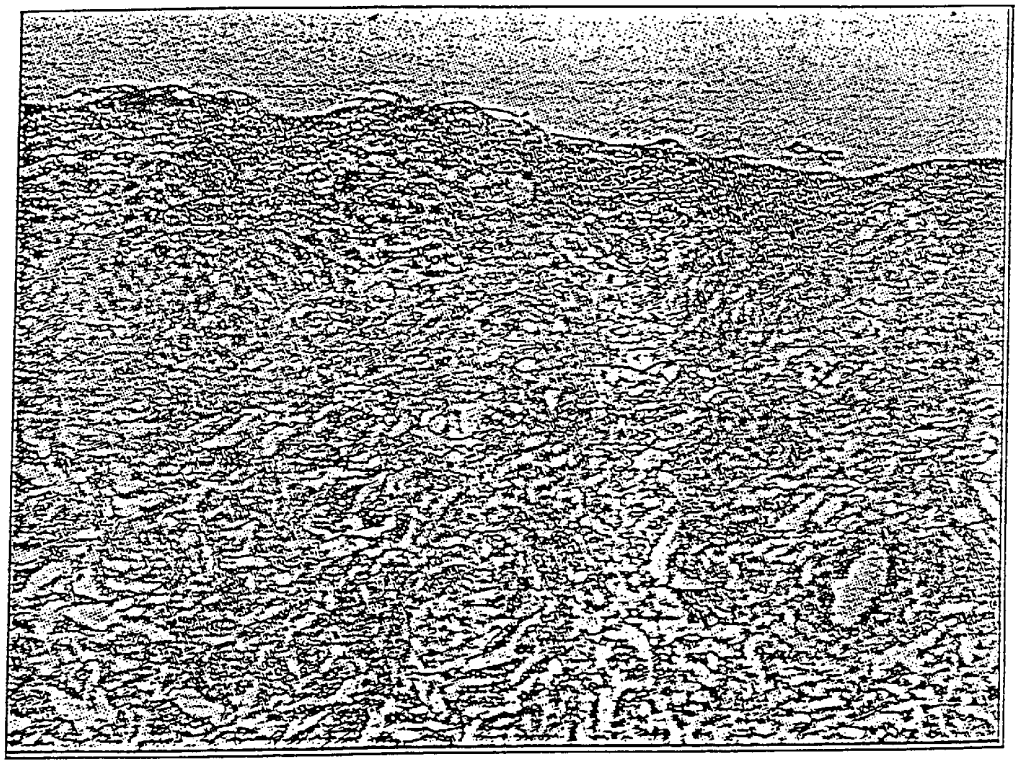


FIG. 3



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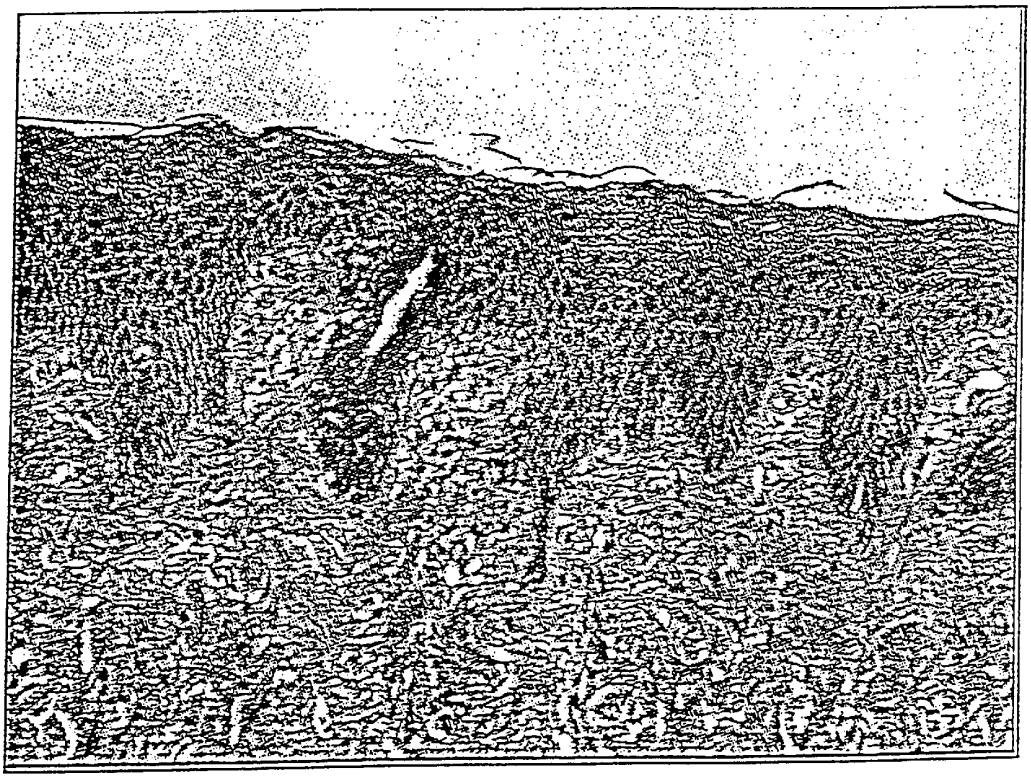


FIG. 5

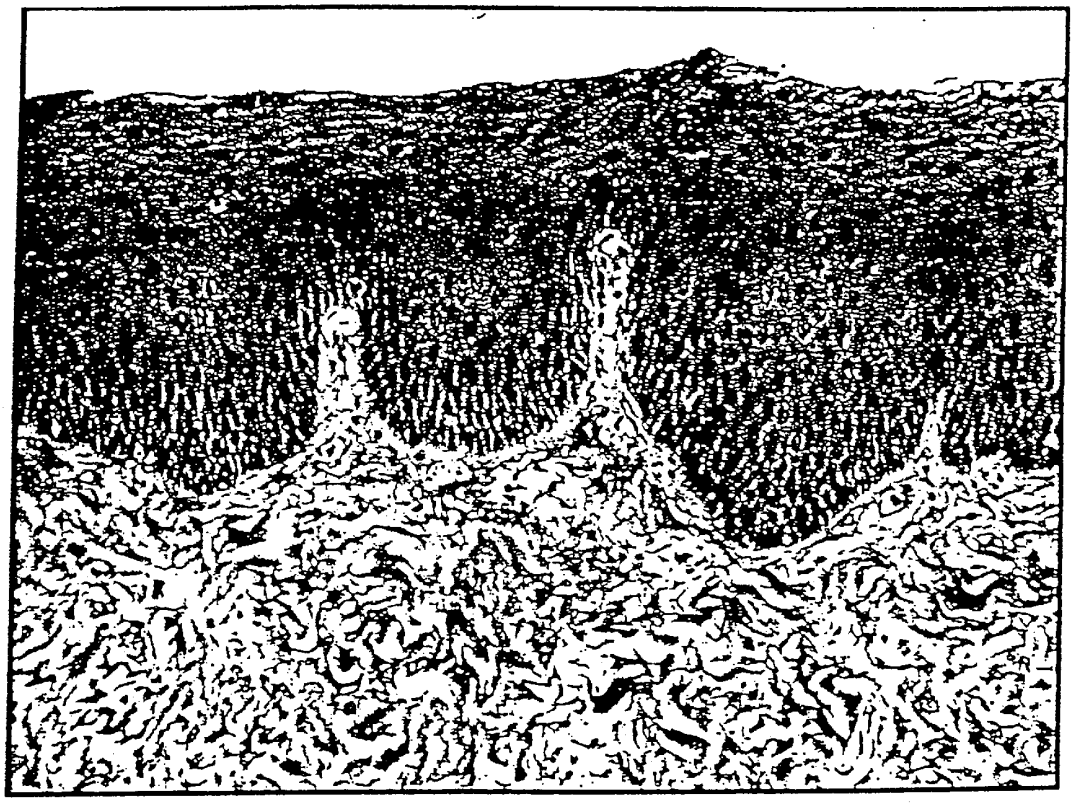


FIG. 6

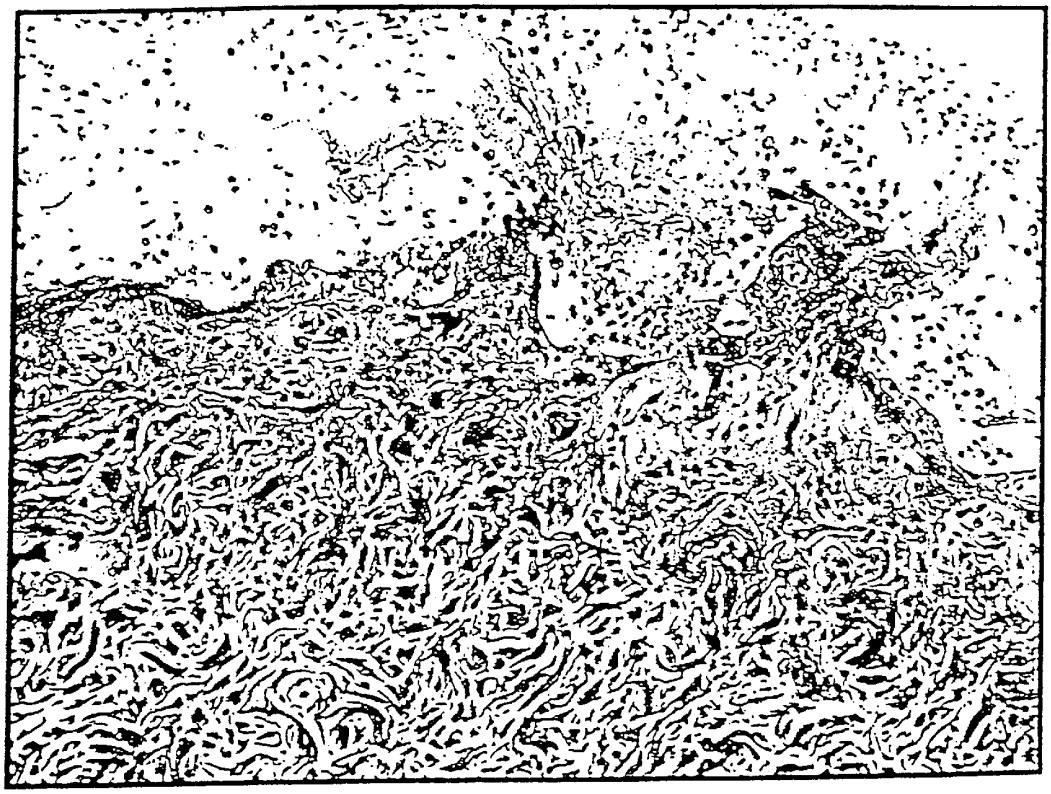


FIG. 7

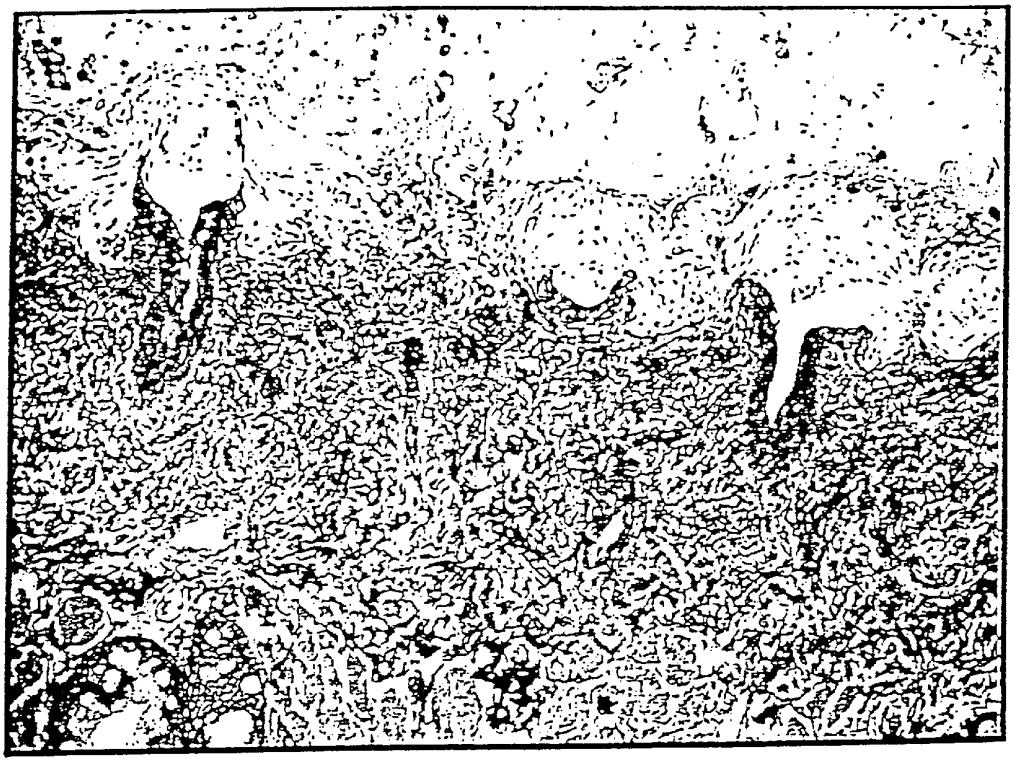


FIG. 8

METHOD FOR INHIBITING BONE RESORPTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 09/134,214, filed Aug. 14, 1998, now U.S. Pat. No. 5,994,329, which is a continuation of PCT/US98/14796, filed Jul. 17, 1998, which claims priority to U.S. Provisional Application Serial No. 60/053,535, filed Jul. 23, 1997 and U.S. Provisional Application Serial No. 60/053,351, filed Jul. 22, 1997, the contents of all of the foregoing of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to oral methods for inhibiting bone resorption in a mammal while minimizing the occurrence of or potential for adverse gastrointestinal effects. These methods comprise orally administering to a mammal in need thereof of a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. The present invention also relates to pharmaceutical compositions and kits useful for carrying out these methods.

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, and hypercalcemia of malignancy. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone disorders caused by or associated with abnormal bone resorption. See H. Fleisch, *Bisphosphonates In Bone Disease, From The Laboratory To The Patient*, 2nd Edition, Parthenon Publishing (1995), which is incorporated by reference herein in its entirety.

At present, a great amount of preclinical and clinical data exists for the potent bisphosphonate compound alendronate. Evidence suggests that other bisphosphonates such as risedronate, tiludronate, ibandronate and zolendronate, have many properties in common with alendronate, including high potency as inhibitors of osteoclastic bone resorption. An older bisphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent bisphosphonates, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization. See Boyce, B. F., Fogelman, I., Ralston, S. et al. (1984) Lancet 1(8381), pp. 821–824 (1984), and Gibbs, C. J., Aaron, J. E.; Peacock, M. (1986) Br. Med. J. 292, pp. 1227–1229 (1986), both of which are incorporated by reference herein in their entirety.

Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. See B. J. Gertz et al., *Clinical Pharmacology of Alendronate Sodium, Osteoporosis Int.*, Suppl. 3: S13–16 (1993) and B. J. Gertz et al., *Studies of the oral bioavailability of alendronate, Clinical Pharmacology & Therapeutics*, vol. 58, number 3, pp. 288–298 (September 1995), which are incorporated by reference herein in their entirety. Intravenous administration has been used to overcome this bioavailability problem. However, intravenous administration is costly and inconvenient, especially when the patient must be given an intravenous infusion lasting several hours on repeated occasions.

If oral administration of the bisphosphonate is desired, relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. To offset this low bioavailability, it is generally recommended that the patient take the bisphosphonate on an empty stomach and fast for at least 30 minutes afterwards. However, many patients find the need for such fasting on a daily basis to be inconvenient. Moreover, oral administration has been associated with adverse gastrointestinal effects, especially those relating to the esophagus. See Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate has been associated with esophageal ulcers. See E. G. Lufkin et al., Pamidronate: *An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International*, 4: 320–322 (1994), which is incorporated by reference herein in its entirety. Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. See P. C. De Groen, et al., *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1016–1021 (1996), D. O. *Castell, Pill Esophagitis—The Case of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1058–1059 (1996), and U. A. Liberman et al., *Esophagitis and Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1069–1070 (1996), which are incorporated by reference herein in their entirety. The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. See C. H. Chestnut et al., *Alendronate Treatment of the Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine*, vol. 99, pp. 144–152, (August 1995), which is incorporated by reference herein in its entirety. Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fall into two categories: (1) those therapies utilizing continuous daily treatment, and (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

The continuous daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily dosing has the potential disadvantage of causing adverse

gastrointestinal effects due to the repetitive, continuous, and additive irritation to the gastrointestinal tract. Also, because bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

Cyclic treatment regimens were developed because some bisphosphonates, such as etidronate, when given daily for more than several days, have the disadvantage of actually causing a decline in bone mineralization, i.e. osteomalacia. U.S. Pat. No. 4,761,406, to Flora et al, issued Aug. 2, 1988, which is incorporated by reference herein in its entirety, describes a cyclic regimen developed in an attempt to minimize the decline in bone mineralization while still providing a therapeutic anti-resorptive effect. Generally, cyclic regimens are characterized as being intermittent, as opposed to continuous treatment regimens, and have both treatment periods during which the bisphosphonate is administered and nontreatment periods to permit the systemic level of the bisphosphonate to return to baseline. However, the cyclic regimens, relative to continuous dosing, appear to result in a decreased therapeutic antiresorptive efficacy. Data on risedronate suggests that cyclic dosing is actually less effective than continuous daily dosing for maximizing antiresorptive bone effects. See L. Mortensen, et al., *Prevention Of Early Postmenopausal Bone Loss By Risedronate, Journal of Bone and Mineral Research*, vol. 10, supp. 1, p. s140 (1995), which is incorporated by reference herein in its entirety. Furthermore, these cyclic regimens do not eliminate or minimize adverse gastrointestinal effects, because such regimens typically utilize periods of multiple daily dosing. Also, the cyclic regimens are cumbersome to administer and have the disadvantage of low patient compliance, and consequently compromised therapeutic efficacy. U.S. Pat. No. 5,366,965, to Strein, issued Nov. 22, 1994, which is incorpoated by reference herein in its entirety, attempts to address the problem of adverse gastrointestinal effects by administering a polyphosphonate compound, either orally, subcutaneously, or intravenously, according to an intermittent dosing schedule having both a bone resorption inhibition period and a no-treatment rest period. However, the regimen has the disadvantage of not being continuous and regular, and requires nontreatment periods ranging from 20 to 120 days. PCT Application No. WO 95/30421, to Goodship et al, published Nov. 16, 1995, which is incorporated by reference herein in its entirety, discloses methods for preventing prosthetic loosening and migration using various bisphosphonate compounds. Administration of a once weekly partial dose of the bisphosphonate is disclosed. However, the reference specifically fails to address the issue of adverse gastrointestinal effects or to disclose administration of larger or multiple dosages.

It is seen from current teachings that both daily and cyclic treatment regimens have shortcomings, and that there is a need for development of a dosing regimen to overcome these shortcomings.

In the present invention, it is found that the adverse gastrointestinal effects that can be associated with daily or cyclic dosing regimens can be minimized by administering the bisphosphonate at a relatively high unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other words, it is found that the administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency. This result is surprising in view of the teachings suggesting that adverse gastrointestinal effects would be expected to increase as a fimction of increasing bisphosphonate dosage. Such administration methods of the present invention would be especially beneficial in treating patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heatburn), ulcers, and other related disorders. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing. Also, patients would not need to keep track of a complex dosing regimen. The methods of the present invention are likely to have the advantage of promoting better patient compliance, which in turn can translate into better therapeutic efficacy.

It is an object of the present invention to provide methods for inhibiting bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods for treating abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods for preventing abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods which are oral methods.

It is another object of the present invention to provide such methods in humans.

It is another object of the present invention to provide such methods in patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heatburn), ulcers, and other related disorders.

It is another object of the present invention to provide such methods while minimizing the occurrence of or potential for adverse gastronintestinal effects.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing interval selected from the group consisting of weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

It is another object of the present invention to provide such methods wherein the continuous dosing schedule is maintained until the desired therapeutic effect is achieved.

It is another object of the present invention to treat or prevent abnormal bone resorption in an osteoporotic mammal, preferably an osteoporotic human.

It is another object of the present invention to provide pharmaceutical compositions and kits useful in the methods herein.

These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to methods for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing, wherein said continuous schedule is maintained until the desired therapeutic effect is achieved for said mammal.

In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

In other embodiments, the present invention relates to methods for treating abnormal bone resorption in a mammal in need of such treatment.

In other embodiments, the present invention relates to methods for preventing abnormal bone resorption in a mammal in need of such prevention.

In other embodiments, the present invention relates to such methods useful in humans.

In other embodiments, the present invention relates to such methods useful in humans indentified as having or being susceptible to upper gastrointestinal disorders.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis-in a mammal.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a human.

In other embodiments, the present invention relates to methods for inhibiting bone resorption, or treating or preventing abnormal bone resorption in a human comprising administering to said human from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

In other embodiments the present invention relates to a pharmaceutical composition comprising from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

All percentages and ratios used herein, unless otherwise indicated, are by weight. The invention hereof can comprise, consist of, or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of simulated gastric juice administered on five consecutive days.

FIG. **2** is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mglmL alendronate in simulated gastric juice administered on five consecutive days.

FIG. **3** is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with a single dosage of 50 mnL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. **4** is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. **5** is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrified 7 days after infusion of the last of 4 separate dosages of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice administered once per week, i.e. once every 7 days.

FIG. **6** is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrified 4 days after infusion of the last of 8 separate dosages of 50 mL of 0.40 mg/mL alendronate in simulated gastric juice administered twice per week, i.e. once every 3–4 days.

FIG. **7** is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL risedronate in simulated gastric juice administered on five consecutive days.

FIG. **8** is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 4.0 mg/mL tiludronate in simulated gastric-juice administered on five consecutive days.

DESCRIPTION OF THE INVENTION

The present invention relates to a method; preferably an oral method, for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse. gastrointestinal effects. The present invention relates to methods of treating or preventing abnormal bone resorption in a mammal in need of such treatment or prevention. The methods of the present invention comprise orally administering to a mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage, wherein said dosage is administered according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days. Typically, the continuous dosing schedule is maintained until the desired therapeutic effect is achieved for the mammal.

The present invention utilizes higher unit dosages of the bisphosphonate at each dosing point than has heretofore been typically administered, yet because of the dosing schedule chosen, the potential for adverse gastrointestinal effects are minimized. Moreover, the method is more convenient because the disadvantages associated with daily dosing are minimized.

The methods of the present invention are generally administered to mammals in need of bisphosphonate therapy. Preferably the mammals are human patients, particularly human patients in need of inhibiting bone resorption, such as patients in need of treating or preventing abnormal bone resorption.

The administration methods of the present invention are especially useful in administering bisphosphonate therapy to human patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. GERD, esophagitis, dyspepsia, ulcers, etc. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

The term "pharmaceutically effective amount", as used herein, means that amount of the bisphosphonate compound, that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the bisphosphonate is a bone resorption inhibiting amount.

The term "minimize the occurrence of or potential for adverse gastrointestinal effects", as used herein, means reducing, preventing, decreasing, or lessening the occurrence of or the potential for incurring unwanted side effects in the gastrointestinal tract, i.e. the esophagus, stomach, intestines, and rectum, particularly the upper gastrointestinal tract, i.e. the esophagus and stomach. Nonlimiting adverse gastrointestinal effects include, but are not limited to GERD, esophagitis, dyspepsia, ulcers, esophageal irritation, esophageal perforation, abdominal pain, and constipation.

The term "abnormal bone resorption", as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. Alternatively, "abnormal bone resorption" can be associated with the formation of bone having an abnormal structure.

The term "bone resorption inhibiting", as used herein, means treating or preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to treatment or prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

The terms "continuous schedule" or "continuous dosing schedule", as used herein, mean that the dosing regimen is repeated until the desired therapeutic effect is achieved. The continuous schedule or continuous dosing schedule is distinguished from cyclical or intermittent administration.

The term "until the desired therapeutic effect is achieved", as used herein, means that the bisphosphonate compound is continuously administered, according to the dosing schedule chosen, up to the time that the clinical or medical effect sought for the disease or condition is observed by the clinician or researcher. For methods of treatment of the present invention, the bisphosphonate compound is continuously administered until the desired change in bone mass or structure is observed. In such instances, achieving an increase in bone mass or a replacement of abnormal bone structure with more normal bone structure are the desired objectives. For methods of prevention of the present invention, the bisphosphonate compound is continuously administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of bone mass density is often the objective. Nonlimiting examples of administration periods can range from about 2 weeks to the remaining lifespan of the mammal. For humans, administration periods can range from about 2 weeks to the remaining lifespan of the human, preferably from about 2 weeks to about 20 years, more preferably from about 1 month to about 20 years, more preferably from about 6 months to about 10 years, and most preferably from about 1 year to about 10 years.

Methods of the Present Invention

The present invention comprises methods for inhibiting bone resorption in mammals. The present invention also comprises treating abnormal bone resorption in mammals. The present invention also comprises methods for preventing abnormal bone resorption in mammals. In preferred embodiments of the present invention, the mammal is a human.

The methods of the present invention do not have the disadvantages of current methods of treatment which can cause or increase the potential for adverse gastrointestinal effects or which require cumbersome, irregular, or complicated dosing regimens.

The present invention comprises a continuous dosing schedule whereby a unit dosage of the bisphosphonate is regularly administered according to a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

By once-weekly dosing is meant that a unit dosage of the bisphosphonate is administered once a week, i.e. one time during a seven day period, preferably on the same day of each week. In the once-weekly dosing regimen, the unit dosage is generally administered about every seven days. A nonlimiting example of a once-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the once-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days falling within two different weekly periods.

By twice-weekly dosing is meant that a unit dosage of the bisphosphonate is administered twice a week, i.e. two times during a seven day period, preferably on the same two days of each weekly period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every three to four days. A nonlimiting example of a twice-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday and Wednesday. It is preferred that the unit dosages are not administered on the same or consecutive days, but the twice-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days within a weekly period or different weekly periods.

By biweekly dosing is meant that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every fourteen days. A nonlimiting example of a biweekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two

dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period, or different monthly periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens have a different periodicity and result in the administration of different numbers of dosages over long periods of time. For example, over a one year period, a total of about twenty four dosages would be administered according to the twice-monthly regimen (because there are twelve calendar months in a year), whereas a total of about twenty six dosages would be administered according to the biweekly dosing regimen (because there are about fifty-two weeks in a year).

In further embodiments or descriptions of the present invention, the unit dosage is given with a periodicity ranging from about once every 3 days to about once every 16 days.

The methods and compositions of the present invention are useful for inhibiting bone resorption and for treating and preventing abnormal bone resorption and conditions associated therewith. Such conditions include both generalized and localized bone loss. Also, the creation of bone having an abnormal structure, as in Paget's disease, can be associated with abnormal bone resorption. The term "generalized bone loss" means bone loss at multiple skeletal sites or throughout the skeletal system. The term "localized bone loss" means bone loss at one or more specific, defined skeletal sites.

Generalized boss loss is often associated with osteoporosis. Osteoporosis is most common in post-menopausal women, wherein estrogen production has been greatly diminished. However, osteoporosis can also be steroid-induced and has been observed in males due to age. Osteoporosis can be induced by disease, e.g. rheumatoid arthritis, it can be induced by secondary causes, e.g., glucocorticoid therapy, or it can come about with no identifiable cause, i.e. idiopathic osteoporosis. In the present invention, preferred methods include the treatment or prevention of abnormal bone resorption in osteoporotic humans.

Localized bone loss has been associated with periodontal disease, with bone fractures, and with periprosthetic osteolysis (in other words where bone resorption has occured in proximity to a prosthetic implant).

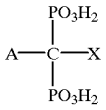
Generalized or localized bone loss can occur from disuse, which is often a problem for those confined to a bed or a wheelchair, or for those who have an immobilized limb set in a cast or in traction.

The methods and compositions of the present invention are useful for treating and or preventing the following conditions or disease states: osteoporosis, which can include post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis; Paget's disease; abnormally increased bone turnover; periodontal disease; localized bone loss associated with periprosthetic osteolysis; and bone fractures.

The methods of the present invention are intended to specifically exclude methods for the treatment and/or prevention of prosthesis loosening and prosthesis migration in mammals as described in PCT application WO 95/30421, to Goodship et al, published Nov. 16, 1995, which is incorporated by reference herein in its entirety.

Bisphosphonates

The methods and compositions of the present invention comprise a bisphosphonate. The bisphosphonates of the present invention correspond to the chemical formula



wherein

A and X are independently selected from the group consisting of H, OH, halogen, NH_2, SH, phenyl, C1–C30 alkyl, C1–C30 substituted alkyl, C1–C10 alkyl or dialkyl substituted NH_2, C1–C10 alkoxy, C1–C10 alkyl or phenyl substituted thio, C1–C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1–C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH_2, C1–C10 alkyl or dialkyl substituted NH_2, OH, SH, and C1–C10 alkoxy.

In the foregoing chemical formula, A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Preferred structures are those in which A is selected from the group consisting of H, OH, and halogen, and X is selected from the group consisting of C1–C30 alkyl, C1–C30 substituted alkyl, halogen, and C1–C10 alkyl or phenyl substituted thio.

More preferred structures are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the group consisting of C1–C30 alkyl, C1–C30 substituted alkyl, Cl, and chlorophenylthio.

Most preferred is when A is OH and X is a 3-aminopropyl moiety, so that the resulting compound is a 4-amino-1,-hydroxybutylidene-1,1-bisphosphonate, i.e. alendronate.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C1–C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

"Pharmaceutically acceptable" as used herein means that the salts and derivatives of the bisphosphonates have the same general pharmacological properties as the free acid form from which they are derived and are acceptable from a toxicity viewpoint.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit

the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those or ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

Nonlimiting examples of bisphosphonates useful herein include the following:

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S. Pat. No. 4,922,007, to Kieczykowski et al., issued May 1, 1990, and 5,019,651, to Kieczykowski, issued May 28, 1991, both of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Pat. No. 4,970,335, to Isomura et al., issued Nov. 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Pat. No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Pat. No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Pat. 4,876,248, to Breliere et al., Oct. 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zolendronate).

Preferred are bisphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

More preferred is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

Most preferred is alendronate monosodium trihydrate.

Pharmaceutical Compositions

Compositions useful in the present invention comprise a pharmaceutically effective amount of a bisphosphonate. The bisphosphonate is typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers, collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups, effervescent compositions, powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs and syrups, effervescent compositions, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, buffers, coatings, and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such a glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is that described in U.S. Pat. No. 5,358,941, to Bechard et al, issued Oct. 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide, and the like.

The precise dosage of the bisphonate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 μg/kg body weight and preferably about 10 to about 2000 μg/kg of body weight.

For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis.

For once-weekly dosing, an oral unit dosage comprises from about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

For twice-weekly dosing, an oral unit dosage comprises from about 8.75 mg to about 35 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of twice-weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 17.5 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 35 mg of the alendronate compound.

For biweekly or twice-monthly dosing, an oral unit dosage comprises from about 35 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of biweekly or twice-monthly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 70 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 140 mg of the alendronate compound.

Nonlimiting examples of oral compositions comprising alendronate, as well as other bisphosphonates, are illustrated in the Examples, below.

Sequential Administration Of Histamine H2 Receptor Blockers And/Or Proton Pump Inhibitors With Bisphosphonates

In further embodiments, the methods and compositions of the present invention can also comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H2 receptor blockers and proton pump inhibitors are well known therapeutic agents for increasing gastric pH. See L. J. Hixson, et al., *Current Trends in the Pharmacotherapy for Peptic Ulcer Disease, Arch. Intern. Med.*, vol. 152, pp. 726–732 (April 1992), which is incorporated by reference herein in its entirety. It is found in the present invention that the sequential oral administration of a histamine H2 receptor blocker and/or a proton pump inhibitor, followed by a bisphosphonate can help to further minimize adverse gastrointestinal effects. In these embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the bisphosphonate. In more preferred embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the bisphonate.

The dosage of the histamine H2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound selected and factors associated with the mammal to be treated, i.e. size, health, etc.

Nonlimiting examples of histamine H2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

Treatment Kits

In further embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium or dietary supplements, either in a form similar to or distinct from the bisphosphonate dosages, can be included to provide a kit in which a dosage is taken every day. In those embodiments including a histamine H2 receptor and/or proton pump inhibitor, these agents can be included as part of the kit.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the invention.

Example 1

Esophageal Irritation Potential

The esophageal irritation potential of the bisphosphonates is evaluated using a dog model.

The experiments demonstrate the relative irritation potential of the following dosing regimens: placebo (Group 1), a single high concentration dosage of alendronate monosodium trihydrate (Group 2), a low concentration dosage of alendronate monosodium trihydrate administered for five consecutive days (Groups 3 and 4), a high concentration dosage of alendronate monosodium trihydrate administered once per week for four weeks (Group 5), a mid-range concentration dosage of alendronate monosodium trihydrate administered twice per week for four weeks (Group 6), a low dosage of risedronate sodium administered for five consecutive days (Group 7), and a low dosage of tiludronate disodium administered for five consecutive days (Group 8).

The following solutions are prepared:

(1) simulated gastric juice (pH about 2), i.e. the control solution.

(2) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

(3) simulated gastric juice (pH about 2) containing about 0.80 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

(4) simulated gastric juice (pH about 2) containing about 0.40 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

(5) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of risedronate sodium on a risedronic acid active basis.

(6) simulated gastric juice (pH about 2) containing about 4.0 mg/mL of tiludronate disodium on a tiludronic acid active basis.

The simulated gastric juice is prepared by dissolving about 960 mg of pepsin (L-585,228000B003, Fisher Chemical) in about 147 mL of 0.90 (wt %) NaCl (aqueous), adding about 3 mL of 1.0 M HCl (aqueous), and adjusting the volume to about 300 mL with deionized water. The pH of the resulting solution is measured and if necessary is adjusted to about 2 using 1.0 M HCl (aqueous) or 1.0 M NaOH (aqueous).

The animals used in the experiments are anesthetized and administered about 50 mL of the appropriate solution over about 30 minutes by infusion into the esophagus using an infusion pump and a rubber catheter. The following treatment experiments are run:

Group 1: This control group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice [solution (1)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 2: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of alendronate [solution (2)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 3: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 24 hours after the dose is administered.

Group 4: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 7 days after the dose is administered.

Group 5: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] once per week, i.e. every seven days, for four weeks. The animals are administered a total of four dosages. The animals are sacrificed about 7 days after the last dose is administered.

Group 6: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.40 mg/mL of alendronate [solution (4)] twice per week, i.e. every three to four days, for four weeks. The animals are administered a total of eight dosages. The animals are sacrificed about four days after the last dose is administered.

Group 7: This group contains eight animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of risedronate [solution (5)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 8: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 4.0 mg/mL of tiludronate [solution (6)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

The esophagus from each sacrificed animal is removed and prepared for histopathology using standard techniques by embedding the tissue in paraffin, staining with hematoxylin and eosin. The sections are examined microscopically. The histopathology results are summarized in Table 1.

For the Group 1 animals (control group), the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. **1** is a representative photomicrograph from a Group 1 animal.

For the Group 2 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **2** is a representative photomicrograph from a Group 2 animal.

For the Group 3 animals, the photomicrographs show that the esophagus has an intact epithelial surface with very slight submucosal inflammation and vacuolation. FIG. **3** is a representative photomicrograph from a Group 3 animal.

For the Group 4 animals, the photomicrographs show that the esosphagus has an intact epithelium with either minimal inflammation (two of the five animals) or no inflammation (three of the five animals) and no vacuolation. FIG. **4** is a representative photomicrograph from a Group 4 animal exhibiting minimal inflammation.

For the Group 5 animals, the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. **5** is a representative photomicrograph from a Group 5 animal.

For the Group 6 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **6** is a representative photomicrograph from a Group 6 animal.

For the Group 7 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. **7** is a representative photomicrograph from a Group 7 animal.

For the Group 8 animals, the photomicrographs show that the esophagus exhibits slight ulceration of the epithelial surface and slight submucosal inflammation and vacuolation. FIG. **8** is a representative photomicrograph from a Group 8 animal.

These experiments demonstrate that considerably less esophageal irritation (comparable to control Group 1)is observed from the administration of a single high concentration dosage of alendronate (Groups 3 and 4) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate considerably less esophageal irritation is observed from the administration of a single high concentration of alendronate on a weekly basis (Group 5) or twice-weekly basis (Group 6) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate that when other bisphosphonates such as risedronate (Group 7) or tiludronate (Group 8) are administered at low dosages on consecutive days that the esophageal irritation potential is high.

TABLE 1

Esophageal Irritation Potential Studies

Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
1 (n = 4)	0	1X daily for 5 days	immediately after last dosing	Normal. Intact epithelium and absence of inflammatory cells in the submucosa.
2 (n = 4)	Alendronate 0.20	1X daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
3 (n = 5)	Alendronate 0.80	1X	24 hours after dosing	Intact epithelial surface with very slight submucosal inflammation and vacuolation.
4 (n = 5)	Alendronate 0.80	1X	7 days after dosing	Intact epithelium with either minimal inflammation (2 of 5 animals) or no inflammation (3 of 5 animals) and no vacuolation.
5 (n = 6)	Alendronate 0.80	1X weekly for a total of 4 doses	7 days after last dosing	Intact epithelium with no inflammation and no vacuolation.

TABLE 1-continued

Esophageal Irritation Potential Studies

Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
6 (n = 6)	Alendronate 0.40	2X weekly for 4 weeks	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
7 (n = 8)	Risedronate 0.20	1X daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface (4 of 8 animals). Marked submucosal inflammation and vacuolation.
8 (n = 4)	Tiludronate 4.0	1X daily for 5 days	24 hours after last dosing	Slight submucosal inflammation and vacuolation (3 of 4 animals, including 1 of these animals with slight ulceration).

Example 2

Once-weekly Dosing Regimen.

Treatment of Osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 3

Twice-weekly Dosing Regimen.

Treatment of Osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis.

Alendronate tablets or liquid formulations containing about 17.5 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 4

Biweekly Dosing Regimen

Treatment of Osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 5

Twice-monthly Dosing Regimen.

Treatment of Osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human twice-monthly, i.e. preferably about once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 6

In further embodiments, alendronate tablets or liquid formulations are orally dosed, at the desired dosage, accord-

ing to the dosing schedules of EXAMPLES 2–5, for treating or preventing other disorders associated with abnormal bone resorption.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2–5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

Example 7

Bisphosphonate Tablets.

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Pat. No. 5,358,941, to Bechard et al., issued Oct. 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

Ingredient	Per Tablet	Per 4000 Tablets
Alendronate Monosodium Trihydrate	45.68 mg	182.72 g
Anhydrous Lactose, NF	71.32 mg	285.28 g
Microcrystalline Cellulose, NF	80.0 mg	320.0 g
Magnesium Stearate, NF	1.0 mg	4.0 g
Croscarmellose Sodium, NF	2.0 mg	8.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

Example 8

Liquid Bisphosphonate Formulation.

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients.

Ingredient	Weight
Alendronate Monosodium Trihydrate	91.35 mg
Sodium Propylparaben	22.5 mg
Sodium Butylparaben	7.5 mg
Sodium Citrate Dihydrate	1500 mg
Citric Acid Anhydrous	56.25 mg
Sodium Saccharin	7.5 mg
Water	qs 75 mL
1 N Sodium Hydroxide (aq)	qs pH 6.75

The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g. about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

What is claimed is:

1. A kit comprising at least one pharmaceutically effective unit dosage of a bisphosphonate selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof, for oral administration to a mammal according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

2. A kit according to claim **1** wherein said mammal is a human.

3. A kit according to claim **2** wherein said unit dosage of said bisphosphonate comprises from about 1.5 to about 6000 ug/kg body weight.

4. A kit according to claim **2** wherein said unit dosage of said bisphosphonate comprises from about 10 to about 2000 ug/kg body weight.

5. A kit according to claim **2** wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

6. A kit according to claim **5** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

7. A kit according to claim **6** wherein said pharmaceutically acceptable salt is a sodium salt.

8. A kit according to claim **7** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

9. A kit according to claim **3** wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

10. A kit according to claim **9** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium , and ammonium salts.

11. A kit according to claim **10** wherein said pharmaceutically acceptable salt is a sodium salt.

12. A kit according to claim **11** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

13. A kit according to claim **14** wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

14. A kit according to claim **13** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

15. A kit according to claim **14** wherein said pharmaceutically acceptable salt is a sodium salt.

16. A kit according to claim **15** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

17. A kit according to claim 5 wherein said unit dosage comprises from about 8.75 to about 140 mg of said bisphosphonate on an alendronic acid active basis.

18. A kit according to claim 17 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

19. A kit according to claim 18 wherein said pharmaceutically acceptable salt is a sodium salt.

20. A kit according to claim 19 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

21. A kit according to claim 2 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

22. A kit according to claim 21 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

23. A kit according to claim 22 wherein said pharmaceutically acceptable salt is a sodium salt.

24. A kit according to claim 3 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

25. A kit according to claim 24 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

26. A kit according to claim 25 wherein said pharmaceutically acceptable salt is a sodium salt.

27. A kit according to claim 4 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

28. A kit according to claim 27 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

29. A kit according to claim 28 wherein said pharmaceutically acceptable salt is a sodium salt.

30. A kit according to claim 2 wherein said bisphosphonate is selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

31. A kit according to claim 30 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

32. A kit according to claim 31 wherein said pharmaceutically acceptable salt is a sodium salt.

33. A kit according to claim 3 wherein said bisphosphonate is selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

34. A kit according to claim 33 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

35. A kit according to claim 34 wherein said pharmaceutically acceptable salt is a sodium salt.

36. A kit according to claim 4 wherein said bisphosphonate is selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

37. A kit according to claim 36 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

38. A kit according to claim 37 wherein said pharmaceutically acceptable salt is a sodium salt.

39. A kit comprising at least one pharmaceutically effective unit dosage of a bisphosphonate selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof, for oral administration to a mammal according to a continuous schedule having a dosing interval of once-weekly dosing.

40. A kit according to claim 39 wherein said mammal is a human.

41. A kit according to claim 40 wherein said unit dosage of said bisphosphonate comprises from about 1.5 to about 6000 ug/kg body weight.

42. A kit according to claim 40 wherein said unit dosage of said bisphosphonate comprises from about 10 to about 2000 ug/kg body weight.

43. A kit according to claim 40 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

44. A kit according to claim 43 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

45. A kit according to claim 44 wherein said pharmaceutically acceptable salt is a sodium salt.

46. A kit according to claim 45 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

47. A kit according to claim 41 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

48. A kit according to claim 47 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

49. A kit according to claim 48 wherein said pharmaceutically acceptable salt is a sodium salt.

50. A kit according to claim 49 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

51. A kit according to claim 42 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

52. A kit according to claim 51 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

53. A kit according to claim 52 wherein said pharmaceutically acceptable salt is a sodium salt.

54. A kit according to claim 53 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

55. A kit according to claim 43 wherein said unit dosage comprises from about 8.75 to about 140 mg of said bisphosphonate on an alendronic acid active basis.

56. A kit according to claim 43 wherein said unit dosage comprises from about 17.5 to about 70 mg of said bisphosphonate on an alendronic acid active basis.

57. A kit according to claim 56 wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

58. A kit according to claim 57 wherein said pharmaceutically acceptable salt is a sodium salt.

59. A kit according to claim 58 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

60. A kit according to claim **56** wherein said unit dosage comprises about 35 mg of said bisphosphonate on an alendronic acid active basis.

61. A kit according to claim **60** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

62. A kit according to claim **61** wherein said pharmaceutically acceptable salt is a sodium salt.

63. A kit according to claim **62** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

64. A kit according to claim **56** wherein said unit dosage comprises about 70 mg of said bisphosphonate on an alendronic acid active basis.

65. A kit according to claim **64** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

66. A kit according to claim **65** wherein said pharmaceutically acceptable salt is a sodium salt.

67. A kit according to claim **66** wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

68. A kit according to claim **40** wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

69. A kit according to claim **68** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

70. A kit according to claim **69** wherein said pharmaceutically acceptable salt is a sodium salt.

71. A kit according to claim **41** wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

72. A kit according to claim **71** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

73. A kit according to claim **72** wherein said pharmaceutically acceptable salt is a sodium salt.

74. A kit according to claim **42** wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

75. A kit according to claim **74** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

76. A kit according to claim **75** wherein said pharmaceutically acceptable salt is a sodium salt.

77. A kit according to claim **40** wherein said bisphosphonate is selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

78. A kit according to claim **77** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

79. A kit according to claim **78** wherein said pharmaceutically acceptable salt is a sodium salt.

80. A kit according to claim **41** wherein said bisphosphonate is selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

81. A kit according to claim **80** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

82. A kit according to claim **81** wherein said pharmaceutically acceptable salt is a sodium salt.

83. A kit according to claim **42** wherein said bisphosphonate is selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

84. A kit according to claim **83** wherein said pharmaceutically acceptable salt is selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

85. A kit according to claim **84** wherein said pharmaceutically acceptable salt is a sodium salt.

86. A kit according to any one of claims **1–85** wherein said unit dosage form is a tablet or capsule.

87. A kit according to claim **86** wherein said kit is a blister pack.

88. A kit according to any one of claims **1–85** wherein said unit dosages are oriented in the order of their intended use.

89. A kit according to claim **88** wherein said unit dosage form is a tablet or capsule.

90. A kit according to claim **89** wherein said kit is a blister pack.

91. A kit according to any one of claim **1–85** wherein said kit comprises a memory aid.

92. A kit according to claim **88** wherein said kit comprises a memory aid.

93. A kit according to claim **89** wherein said kit comprises a memory aid.

94. A kit according to claim **90** wherein said kit comprises a memory aid.

* * * * *

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

Merck & Co., Inc.

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) ATTORNEYS (FIRM ADDRESS AND TELEPHONE NUMBER)
Mary B. Graham
MORRIS, NICHOLS, ARSHT & TUNNELL LLP
1201 North Market Street; P.O. Box 1347
Wilmington, DE 19899-1347
302-658-9200

DEFENDANTS

Apotex, Inc.

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN "X" IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated or Principal Place of Business in This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated and Principal Place of Business in Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (PLACE AN "X" IN ONE BOX ONLY)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgement
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholder Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault Libel & Slander
- ☐ 330 Federal Employers Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

HABEAS CORPUS:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R R & Truck
- ☐ 650 Airline Regs
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl Ret Inc Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks or Banking
- ☐ 450 Commerce/ICC Rates/etc
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

V. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

- ☒ 1 Original Proceeding
- ☐ 2 Removed From State Court
- ☐ 3 Remanded From Appellate Court
- ☐ 4 Reinstated or Reopened
- ☐ 5 Transferred From another district (specify) ____
- ☐ 6 Multidistrict Litigation
- ☐ 7 Appeal to District Judge from Magistrate Judgement

VI. CAUSE OF ACTION

(CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE BRIEF STATEMENT OF CAUSE DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY)

Suit for patent infringement under 35 U.S.C. § 271.

VII. REQUESTED IN COMPLAINT

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ YES ☒ NO

VIII. RELATED CASE(S) IF ANY (See Instructions)

JUDGE Joseph J. Farnan, Jr. / Gregory M. Sleet

DOCKET NUMBER 00-035, 00-052, 01-048, 05-366
DOCKET NUMBER 04-939, 05-658

DATE 4/7/06

SIGNATURE OF ATTORNEY OF RECORD Mary B. Graham

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 06-230

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 1 COPIES OF AO FORM 85.

4/7/06
(Date forms issued)

(Signature of Party or their Representative)

Chris Talley
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action